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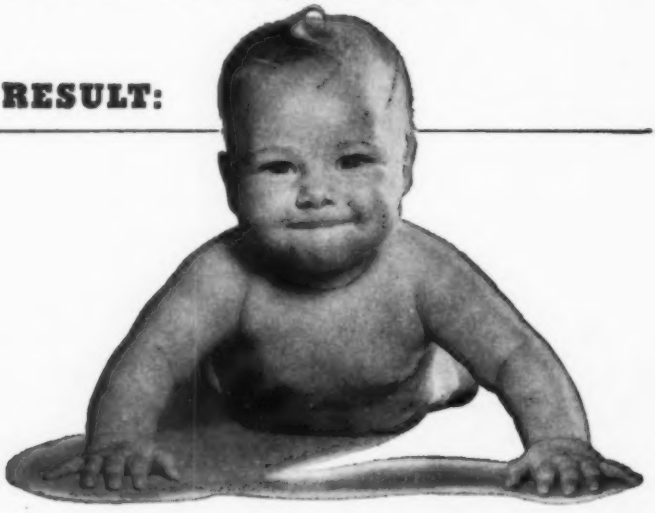

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The Journal of Pediatrics

VOL. 44 FEBRUARY, 1954 NO. 2

TONSILLECTOMY AND ADENOIDECTOMY

A RE-EVALUATION OF RESULTS

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DURING the past thirty years there has been an increasing conservatism in arriving at the decision to remove tonsils and adenoids. While this has been accentuated by the advent of chemotherapy, the trend was evident even before that. In our own clinic, whose composition would reflect that of an average office practice in the middle economic stratum, the ratio of tonsillectomies to outpatients fell from 1:20 in 1936 to 1:50 in 1952. In a private school, whose students we have checked for twenty-five years, but who had their own private physicians, 75 per cent had had a tonsillectomy by the age of 12 twenty years ago; in the present student body, 25 per cent had had the procedure by the sixth year, and at the present rate, it may be expected that only an additional 14 per cent will have had it in the next twelve years. Undoubtedly in the prechemotherapy era the procedure was often resorted to in the hope that, even if the number of infections were not reduced, involvement of the ear might be lessened. But aside from this, considerations of sacrificing a tissue that might play an active role in the development of immunity,[1, 2] failure to show a significant difference in the incidence of infection in the age group 5 to 7,[3] disappointing results when the allergic state was confused with the infectious,[4] and a greater appreciation of the normal involution of this tissue when mere size was a consideration, have all played roles in a more temporizing attitude. And yet we think there are few procedures whose results are more gratifying when the indications are met, and we have a feeling that the pendulum may have swung too far to the conservative side.

The present appraisal was arrived at by (1) circularizing about 1,000 parents, of whom approximately 600 gave satisfactory replies, for their own opinion on the effect of the removal on specific complaints; (2) by rechecking several groups of patients with conditions thought to be influenced by chronic infection, and (3) by a small series of metabolic studies before and after the procedure. At the time of operation, there was inserted in the child's record a sheet listing the specific reason for the procedure concurred in by pediatrician and otolaryngologist. In the follow-up questionnaire, the parents were asked whether the particular com-

From the Department of Pediatrics, Henry Ford Hospital.

plaint had been relieved. Since no statistically significant difference (by the chi square method) was noted between the two-year and the nine-year follow-up, except in the cases of asthma and bronchitis, the results are graphed together.

Discordant results in the literature may be related to a variety of factors. In the middle economic stratum, nutritional failure can be more clearly related to disease than to the availability of adequate food.[5] In a sampling of 100 cases of malnutrition in this group, failure to gain normally could be related to a poor diet in only four cases; hence an improved nutritional state following tonsillectomy could be more clearly attributed to the procedure than in a poor economic group where poor diet was an uncontrolled variable. This may explain the better results reported in four series involving 700 cases[6] from private practice than found in Kaiser's series from the dispensary group.

The age at which the procedure was carried out might be expected to influence end results. There would appear to be an irreducible minimum of respiratory infections incidental to daily group contact in the first few years of school independent of the presence or absence of tonsils. This is reflected in Fig. 1. Kaiser's cases were operated in the years 5 to 7. Epstein's[7] 540 cases were divided into the age groups 2 to 6, 7 to 10, and 11 to 13, with about 20 per cent in the younger and older age groups. Except for tonsillitis and pharyngitis, the results of the procedure on all complaints were only fair in the youngest as compared with the two older groups.

SELECTION OF CASES

Aside from obvious obstruction and persistent cervical adenitis, it must be admitted that the basis for the diagnosis of chronic infection is more inferential than objective. Cryptic appearance, size, injection of pillars have all failed to correlate with the findings on removal, and we have had the experience common to others of finding frank abscesses in tonsils so small as to be scarcely visible. We have therefore seldom been willing to make the decision on removal until after a period of observation of months and sometimes years. This makes possible, by providing data for a growth curve, a more valid assessment of nutrition than would derive from an isolated comparison of weight and height with a mean for age. An adenitis that disappears in a few months would cease to have the significance attached to a truly chronic one. A partial obstruction to breathing will often disappear with deepening of the nasopharynx. Denzer and Felshin's[8] study of 217 children in a "pretonsillectomy clinic" showed only 17 per cent ultimately referred for tonsillectomy, other causes for their complaints being adduced with more complete study, and many of them proving transient. In Day's[9] study of 252 children on a waiting list for eighteen months, 37 per cent seemed no longer to have the indication for the procedure which originally existed.

RESULTS

The results are recorded in Table I and in Figs. 1 and 2.

1. *Frequency of Respiratry Infections.*—It is difficult to reconcile the

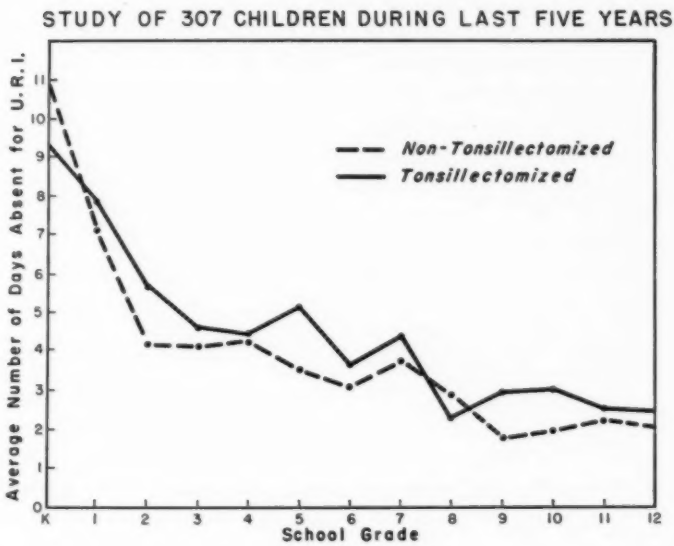
STUDY OF 307 CHILDREN DURING LAST FIVE YEARS
Average Number of Days Absent for U.R.I.
Non-Tonsillectomized
Tonsillectomized
School Grade
K 1 2 3 4 5 6 7 8 9 10 11 12

Fig. 1.

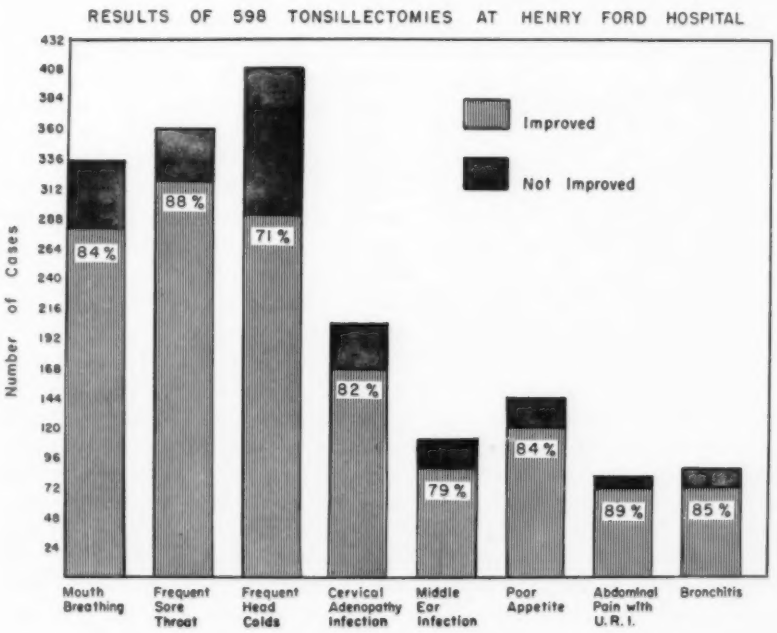
RESULTS OF 598 TONSILLECTOMIES AT HENRY FORD HOSPITAL
Number of Cases
Improved
Not Improved
84 %
88 %
71 %
82 %
79 %
84 %
89 %
85 %
Mouth Breathing
Frequent Sore Throat
Frequent Head Colds
Cervical Adenopathy Infection
Middle Ear Infection
Poor Appetite
Abdominal Pain with U.R.I.
Bronchitis

Fig. 2.

highly favorable report of parents on this item with the negative conclusion drawn from a comparison of tonsillectomized school children. One would have to assume that they failed to credit the normal decline in frequency that is a function of the passage of time. That one might expect the removal of a focus of infection to result in a reduced incidence implies that some throat infections represent endogenous reactivations. Since the Selye concept of the role of stress phenomena in depressing the immune reaction, this has a more rational basis, and we are constantly impressed with the frequency with which trauma, head injury, exposure and fatigue have been followed by acute throat infections. Improvement in ear infections (71 per cent) is a more favorable result than reported by Kaiser, but comparable with that of Selkirk and Mitchell.[10]

TABLE I. AGE DISTRIBUTION IN TWO FOLLOW-UP GROUPS

	NUMBER OF YEARS FOLLOWED	
	9 YEARS	2 YEARS
Number of cases	503	95
Per cent ages 1 to 4	18	23
Per cent ages 5 to 7	56	52
Per cent ages 8 to 14	26	25

Since there was no statistically significant difference in the end results after two and nine years, except for bronchitis and asthma, the data are combined in the graphic charts.

2. *Abdominal Pain Referable to Chronic Throat Infection.*—There were seventy-two cases in which the procedure was done to influence the complaint of abdominal pain with 89 per cent reporting improvement. While Brennemann[11] pointed out the role of the throat in the causation of acute episodes, we do not feel that the entity of chronic epigastric distress, with anorexia and, in particular, aversion from the morning meal, in association with chronic throat infection is as widely accepted as is warranted by its frequency. In a large number of these we had barium studies which rather consistently showed pylorospasm and delayed emptying. In this clinic, an analysis of the complaints of 500 new patients, usually coming for another opinion, showed an incidence of abdominal pain as the chief complaint in 7.2 per cent. A thorough survey to exclude other causes, notably genitourinary, having been done, the most common cause for this in the child under 10 would appear to be chronic lymphoid infection, involving the nasopharyngeal ring but also the mesenteric nodes.

3. *Bronchitis.*—While in the average of all age groups 85 per cent showed improvement in this complaint, there was an age difference. In the group under 4 years, ten of sixteen were improved, while in the older groups, sixty-four out of seventy-one reported improvement. In Kaiser's[3] series, there was an actual increase. Selkirk and Mitchell[10] showed frequent cough to be less common after the operation, but observed that bronchitis decreased with age in any case and remained an uncontrolled variable.

4. *Sinus Infection.*—In only thirteen of twenty-eight cases was improvement noted. Selkirk and Mitchell[10] found eight relieved, nine unimproved, and eleven cases newly developed. Griffiths[12] in 5,000 cases found sinusitis more common in tonsillectomized children. From a study of the lymphatic drainage of the sinuses of dogs with vital dyes, he suggested that one function of the tonsil

was to receive drainage from the sinuses. Kaiser[3] similarly found sinusitis more common in the tonsillectomized. This is a difficult point to assess. In 100 cases at this hospital in whom tonsillectomy seemed indicated on other grounds, there was x-ray evidence of sinusitis in fifty before the operation, though clinically this diagnosis had not been made. In the absence of tonsils and adenoids, one is more likely to seek in the sinuses for the cause of respiratory complaints. Probably they share in any severe degree of infection of the upper respiratory tract and cannot be clearly dissociated from the rest of the area.

5. *Asthma.*—The results of tonsillectomy on this condition in our own experience, and from the reports in the literature, have been so unsatisfactory that the number on whom it was done was small. However, we have seen occasional brilliant results in the older child whose nutritional state was impaired and in whom the history was clear that tonsillar infection always preceded the attacks of asthma. The procedure was carried out on thirty-one asthmatics. In the youngest group, two of four improved, in the middle group (5 to 7 years), eleven of fifteen improved, and in the older group (8 to 14 years) five of seven improved. Considering separately, however, a group of twenty-two asthmatics with long follow-up, seven gave a history that asthma appeared for the first time shortly after the tonsillectomy, seven had had it before the procedure and were not benefited, and five felt they were worse. In only three was there improvement, and that had lasted not longer than nine months.

In Hedstrom's[4a] series of fifty-two cases, eight improved, four were worse, and forty showed no change. Clein, Finegold, Waldbott and Ascher, and Hansel and Chang[4] show similar results in almost 1,500 allergic and asthmatic cases. All emphasize the importance of careful appraisal to exclude this group. Our seemingly good results might be ascribed to the careful selection of those who had reasons for tonsillectomy other than asthma, notably an impaired nutritional state. It would still seem illogical to us to embark on a program of hyposensitization with bacterial vaccines in the presence of infected tonsils in a child over eight whose attacks are always precipitated by infection.

6. *Appetite and the Nutritional State.*—There was a complaint of anorexia in 144 cases, and of these 84 per cent reported improvement. An additional forty-two cases in whom anorexia was not recorded as the indication volunteered the statement that appetite had improved. It was considered that the alleged anorexia was significantly related to tonsils only when there was a concomitant failure of weight gain. Marked gain in weight following tonsillectomy has long been noted,[3] but it has not been established that this weight gain actually reflected an improved nutritional state as judged by the storage of nitrogen and calcium. We have previously reported studies[5] on nine children in whom the nitrogen retention improved from an average of 0.06 gram per day to the normal figure of 1.52 grams per day. An additional balance study is recorded here in which the calcium was also determined.

An 8-year-old girl with a tuberculous knee was a candidate for fusion when the procedure was deferred because of osteoporosis and a balance study conducted for eighteen days before and twenty-seven days after the removal of infected tonsils. The results are recorded in Table II. It will be noted that there is a threefold increase in the storage of both nitrogen and calcium, the economy in the latter referable to marked reduction in fecal loss.

7. *Recurrent Vomiting.*—In a previous study of a group of fifty children with this condition[14] a large number of etiological factors could be demonstrated, but in twenty-one, infected tonsils seemed to play the chief role, and the number and severity of attacks were reduced by removal in seventeen cases. In this group, the history told of the association of the attacks with acute throat infection, and metabolic studies between attacks suggested that as a result of the infection, these children showed metabolic mixtures (high protein, high fat and low carbohydrate) leaving them on the verge of ketosis. Before this decision is reached in a given case, full consideration should be given to other causative factors, notably the emotional ones, since in this group a major surgical procedure can be very traumatic.

8. *Miscellaneous.* — Impaired hearing was benefited in seven of nine cases. In the occurrence of acute hemorrhagic nephritis, the presence or absence of tonsils seemed to play no role. In a series of sixty, half had already had the procedure. The removal in the hope of influencing the subacute or chronic case has given mixed results. In one case, red cells immediately disappeared from the urine; in another an acute exacerbation followed.

In eight of ten cases of infectious arthritis, improvement followed removal.

TABLE II. EFFECT OF REMOVAL OF TONSILS AND ADENOIDS ON NITROGEN AND CALCIUM BALANCE

	NITROGEN (GRAMS/DAY)				CALCIUM (GRAMS/DAY)			
	AVERAGE URINE	AVERAGE STOOL	INTAKE	BALANCE	AVERAGE URINE	AVERAGE STOOL	INTAKE	BALANCE
18-day control	8.32	1.08	9.77	+0.43	0.001	0.832	0.903	+.069
27-day postoperative	7.06	0.91	9.55	+1.24	0.068	0.548	0.907	+.210

SUMMARY AND CONCLUSIONS

From a follow-up study of 598 cases, and from a review of several conditions thought to be influenced by tonsillectomy and adenoidectomy, it is concluded that the procedure remains a highly beneficial one in the properly selected case. It is stressed that the decision to remove can be arrived at only after a sufficiently long period of observation has excluded other causes for the complaint.

REFERENCES

1. Dougherty, I. F., Chase, J. H., and White, A.: The Demonstration of Antibodies in Lymphocytes, Proc. Soc. Exper. Biol. & Med. **57**: 295, 1944.
2. Erich, W. E., and Harris, T. N.: The Formation of Antibodies in the Popliteal Lymph Nodes in Rabbits, J. Exper. Med. **76**: 335, 1942.
3. Kaiser, Albert D.: The Relation of Tonsils and Adenoids to Infection in Children, Am. J. Dis. Child. **41**: 568, 1931.

4. a. Hedstrom, V: Experiences of Tonsillectomy in Bronchial Asthma, Acta Allergol. 3: 147, 1950.
   b. Clein, Norma W.: Allergy in the Tonsil Problem in Children, Ann. Allergy 7: 329, 1949.
   c. Finegold, Ben. F.: Tonsillectomy in the Allergic Child, California Med. 71: 341, 1949.
   d. Waldbott, G. L., and Ascher, M. S.: Results of Tonsillectomy in Allergic Patients, Tr. Am. Therap. Soc., p. 82, 1936.
   e. Hansel, French K., and Chang, C. S.: Relation of Allergy and Tonsillectomy in Children. Incidence of Respiratory Allergy in Cases of Routine Tonsillectomy, Arch. Otolaryng. 31: 45, 1940.
5. Johnston, J. A., and Maroney, J. W.: Focal Infection and Metabolism, J. PEDIAT. 12: 563, 1938.
6. a. Guymer, R. F.: Tonsillectomy: Before, During and After, Brit. J. Child. Dis. 31: 85, 1945.
   b. Smith, Harold D.: Follow-up of Patients 8 Months After Tonsillectomy, Arch. Otolaryng. 24: 488, 1936.
   c. Bass, M. H.: Results of Tonsillectomy in Private Practice, Laryngoscope 44: 780, 1934.
   d. Hadfield, H.: The Tonsil Problem, J. Laryng. & Otol. 64: 598, 1950.
7. Epstein, I. M.: Factors Influencing the Results of Tonsillectomy and Adenoidectomy, Am. J. Dis. Child. 53: 1503, 1937.
8. Denzer, Bernard S., and Felshin, Gertrude: The Pretonsillectomy Clinic, J. PEDIAT. 22: 239, 1943.
9. Day, David L.: Survey of 681 Children Awaiting Tonsillectomy and the Indications for Operation in Childhood, M. J. Australia 1: 39th yr., No. 15, p. 510.
10. Selkirk, Theodore K., and Mitchell, A. Graeme: Evaluation of the Results of Tonsillectomy and Adenoidectomy, Am. J. Dis. Child. 42: 9, 1931.
11. Brennemann, J.: The Abdominal Pain of Throat Infections in Children and Appendicitis, J. A. M. A. 89: 2183, 1927.
12. Griffiths, Ivor: Function of the Tonsils and Their Relation to the Aetiology and Treatment of Nasal Catarrh, Lancet 2: 723, 1937.
13. Paterson, D., and Bray, G. W.: Tonsillar Hypertrophy and Infection as a Factor in Ill-Health, Lancet 2: 1074, 1928.
14. Johnston, J. A., and Mason, R. J.: Metabolic and Clinical Observations on Fifty Children Subject to Recurrent Attacks of Vomiting, International Clinics, vol. IV, series 48, Philadelphia, 1938, J. B. Lippincott Co.

HYPOTHERMIA IN CARDIAC SURGERY

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INTEREST in hypothermia and its effects upon living tissue did not develop as a contemporary phenomenon. No one knows the antiquity of curiosity in regard to the ability of hibernating animals to so arrange their bodily economy that prolonged suspension of activity without renewal of energy stores, and with no discernible stress, is possible. This facility of survival is now recognized to be due to the special property of maintenance of vital tissue function at a very low metabolic rate. The importance of the hibernating animals' reduced temperature as a determining factor in the effectiveness of the low metabolic rate may be accepted without question of the validity of many observations.

The use of induced hypothermia in the solution of problems in human disease has aroused surprisingly little thought until recently. Temple Fay[1-6] was the early apostle of its value but his work was appreciated by few. Intrigued by the possibility that cancer cells may require a favorable temperature for growth, he began a series of observations which indicated that lowering of body temperature was effective in retarding the growth of neoplastic tissue and in reducing or abolishing painful sensations.

Later, Talbott[7-9] subjected severely psychotic patients to a reduction in body temperature. The effect on the mental disturbance was transitory but conclusions of great physiologic importance were gained from the studies.

Hypothermia in relation to cardiac surgery requires mention of the work of McQuiston.[10-12] Concern in regard to the deleterious effects of hyperpyrexia during surgery caused his attention to be turned to the problem of deliberate lowering of body temperature. He was able to report very encouraging results of the application of moderate cooling in a series of cyanotic individuals subjected to great vessel or cardiac operations.

These observations, and a large body of experimental material reported over many years, encouraged our initial studies of the possibilities of hypothermia as an aid in cardiac surgery. They were intended, in part, to complement our investigations in the field of extracorporeal circulation.

Bigelow and his associates[13-15] had published the results of their experiments with hypothermia. They demonstrated that lowering of the temperature of dogs from 38° to 18° C. (100.4° to 64.4° F.) decreased metabolism and oxygen demand significantly. Extending their studies, they showed that dogs can survive occlusion of both venae cavae for at least

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Aided by grants from The Mary Bailey Foundation and the United States Public Health Service.

fifteen minutes, during which time the left atrium may be opened. However, of the thirty-nine dogs studied, only twenty (51.2 per cent) were revived to normal temperature. Six of these ultimately survived (15.3 per cent), the remaining animals dying of shock appearing two to twelve hours later.

We decided to repeat certain of Bigelow's procedures and to try to solve, if possible, some of the problems encountered by his group.[16]

ANIMAL EXPERIMENTS

Series 1.—Sixteen dogs were used. They enabled us to become familiar with the process of body cooling and with the behavior of the heart at low temperature.

Series 2.—Twenty-seven dogs were studied. They were cooled to 24° to 26° C. (75.2° to 78.8° F.). The venae cavae were occluded in each dog for twelve minutes. In eight the right atrial wall was incised and the interior of the chamber widely exposed by traction on stay sutures. The right atrium was leisurely explored under direct vision. At the expiration of the allowed period, the incision was closed by one or two rows of sutures. In ten animals a similar incision was made in the right ventricle. Of the twenty-seven animals, twenty-three (85.1 per cent) survived the entire procedure. This marks a great improvement over Bigelow's results. Weeks to months later, ten of these dogs were subjected to cardiodynamic, hematologic, and blood chemical studies and were sacrificed for extensive morphologic tissue investigation.[17]

This series is actually comprised of two groups. The first (eleven ventriculotomies) received atropine (0.04 to 0.08 mg. per kilogram) and morphine sulfate (1 mg. per kilogram) intraperitoneally, followed in thirty minutes by Pentothal Sodium (30 mg. per kilogram) intravenously. Cooling was accomplished in a commercial beverage cooler. Respirations were controlled by means of an automatic respirator supplying 100 per cent oxygen. ACTH, penicillin, and 50 per cent glucose were administered. If shivering was observed, an additional dose of 50 mg. of Pentothal Sodium was injected intravenously. When the temperature had reached the desired level, the animal was prepared for surgery. Following thoracotomy, 10 c.c. of 1 per cent procaine hydrochloride was injected into the pericardial sac. The azygos vein was ligated and umbilical tapes were placed loosely about the cavae. The planned operation then proceeded, the cavae being occluded by clamps. After the desired period of occlusion, the superior vena cava was released. Benodaine (0.8 mg. per kilogram) was injected into the right ventricle. Five minutes later the inferior vena cava was partially released. Benodaine was again injected after five minutes and the inferior vena cava completely released. Following insertion of a drainage tube and closure of the chest, penicillin, thiamine chloride, and 50 per cent glucose were given. The animal was rewarmed over a period of three hours by means of an electric blanket. Oxygen was administered continuously. Another dose of 50 per cent glucose was given on recovery.

The second group (eight atriotomies, eight ventriculotomies) received morphine sulfate and atropine sulfate subcutaneously and the initial dose of

Pentothal Sodium was decreased. Digitoxin (0.014 mg. per kilogram) was given prior to beginning the experiment, and Vasoxyl intravenously in small doses was given throughout the period of surgery. In addition, a second dose of atropine sulfate was given if bradycardia was noted. Thiamine chloride was administered before rather than after surgery, and 50 per cent glucose was given immediately before thoracotomy as well as at the initiation of hypothermia and before rewarming. Benodaine was withheld after releasing the superior vena cava until it was ascertained that the heart was beating satisfactorily (32 per minute or more) with no sign of block. Then 0.6 mg. per kilogram was injected; 90 seconds later the inferior vena cava clamp was partially removed; two to three minutes later the vessel was released completely. If the heart beat satisfactorily for 10 minutes, the pericardial sac and chest wall were closed.

A word is necessary in regard to the use of Benodaine. It had been observed in early experiments that ventricular fibrillation frequently followed release of the caval clamps. Initially, the heartbeat would become vigorous and rapid but very shortly this lethal arrhythmia would appear. It was suggested by Dr. Nicholas Dreyer, who was visiting in the laboratory, that epinephrine might be responsible. During occlusion of the inferior cava, this substance would be accumulating, its discharge from the adrenal being induced by relative anoxia. With release of the clamp, a large charge pouring into the heart might very likely induce ventricular fibrillation. This suggested the use of Benodaine to counteract the effect.

Two deaths occurred in each group. The first animal developed heart block following twelve minutes of caval occlusion. After thirty minutes, alternating compression and release of the heart was instituted. The heart block disappeared. Twenty-one hours later the animal died of shock. The administration of Benodaine in the routine fashion had probably been an evil factor here. Cardiac standstill during surgery occurred in the second dog. No Benodaine was given and the inferior caval clamp was released to give the animal the advantage of his own epinephrine. Ventricular fibrillation ensued and we were unable to halt the process. The third death was due to gross hemorrhage many hours after completion of the experiment. The fourth, also occurring many hours postoperatively, cannot be etiologically explained.

Series 3.—Five dogs comprised this group. In Series 1 it had been found that WIN 2173* (an isoquinoline derivative) appeared to correct the severe bradycardia (heart rate of 3 to 6 per minute) of profound hypothermia. WIN 2173 was used in these five animals which were cooled to 17° C. (62.6° F.) and the cavae occluded for thirty minutes. In each, right atriotomy was performed, the chamber being open for approximately twenty minutes. The heart beat regularly throughout the procedure. Two animals survived, two died of ventricular fibrillation, and one was accidentally killed. Encouragement, but no conclusions, derive from this series. Further study is in progress.[18]

*Winthrop Stearns Company.

Series 4.—This group, although large, is of little value in regard to numbers and percentages. Following the development of the routines outlined in Series 2, there was a period of somewhat disorganized research during which various men on the thoracic service, new to the technique, applied it to the problem of creating and repairing atrial septal defects in dogs. Too, spur-of-the-moment physiologic and pharmacologic measures were tried, all enthusiastically calculated to ensure the absolute safety of the procedure, but inevitably, by diabolic mischance, ending in the death of the animal. The causes of death were many: coronary air embolism causing intractable ventricular fibrillation, damage to the conducting system, thrombosis, shock, and hemorrhage.

Series 5.—Ten dogs were studied. The temperature was reduced to 26° C. (78.8° F.). Following occlusion of the cavae, right atriotomy was performed in each case. A defect was then created in the interatrial septum and the left heart chambers were explored digitally. After a short period the defect was repaired by suturing. During the time of exposure of the left atrium an arterial transfusion was given under constant pressure (70 mm. Hg). We feel that this serves to nourish the coronary arteries and brain and to prevent air embolism.[19] The material used for the transfusion is a suspension of erythrocytes in Ringer gelatin* solution (ERG solution).[20] Of the ten animals operated upon in this manner, nine survived. Air embolism occurred in the single animal which died, due to failure to maintain the arterial transfusion at the proper rate of flow.

Series 6.—Three dogs were cooled to 21° to 24° C. (69.8° to 75.2° F.). Heart and lungs were removed en bloc and organs from donor animals substituted. One animal survived for six hours, with return of reflexes, spontaneous respiration, and a normal electrocardiogram.[21] The results of this experiment are stimulating.

From this body of work it was obvious that controlled reduction of temperature in dogs was safe. It was also clear that at a temperature as low as 26° C. (78.8° F.) the circulation could be interrupted for at least twelve minutes and the heart opened with surprisingly few pathologic sequelae in the surviving dogs. It seemed, too, to have been demonstrated that arterial transfusion would be of great help in preventing air embolism and affording nourishment to the myocardium and brain during cardiotomy with exposed left chambers.

CLINICAL APPLICATION

After certain of the investigations detailed above, a clinical problem was presented which appeared to demand for its solution the use of hypothermia.

CASE 1.—H. D., a 30-year-old female, for the past five years had had progressive diminution in exercise tolerance and frequent eposides of paroxysmal auricular tachycardia. Catheterization gave evidence of an atrial septal defect. Pulmonary artery pressure was normal. Exploratory palpation of the atrial septum via the right atrial appendage showed a large defect immediately above the atrioventricular valves and a smaller defect in the region of the fossa ovalis. The chest was closed. On Aug. 29, 1952, operation was performed under hypothermia. Surgery was started at 27.2° C. (81° F.). The lowest tem-

*Modified Fluid Gelatin No. 8, Knox Gelatin Co., Camden, N. J.

perature was 25.8° C. (78.5° F.). Through a right atrial incision with the cavae, pulmonary artery, and aorta clamped for six minutes, both defects were closed by sutures, the lower one incompletely. Cardiac infusion of Ringer's solution was given constantly. Ventricular fibrillation began after five minutes of caval occlusion. Resuscitory measures were fruitless.

Comment: Closure of this patient's defect was considered necessary because of progression of symptoms. When exploration revealed the nature of the defect, the technique of atrio-septo-pexy[22] was thought to be impossible of application. Hypothermia, interruption of circulation, and direct suturing with an open atrium seemed indicated. Reduction of temperature to 27.2° C. (81° F.) required nine and one-half hours. This long period, with its progressively increasing effect on the myocardium, may have contributed to the unfortunate outcome, although heart action and blood pressure at the time of thoracotomy were satisfactory. Coronary air embolism probably was an important factor. In addition, the reflex responses to clamping of the ascending aorta may conceivably have played a role.

Since that time, fifteen additional patients in whom hypothermia was used as an adjunct to anesthesia have been operated upon. Two also had atrial septal defects.

CASE 2.—J. S., an 11-year-old female, had had decreased exercise tolerance which was progressive since age 5, with frequent episodes of palpitations, syncopal attacks during the last four months, and increasing cardiac size. Catheterization gave evidence of an atrial septal defect. Pulmonary artery pressure was slightly increased. At operation, Sept. 19, 1952, under hypothermia, the lowest temperature reached was 31.1° C. (88° F.) after several hours. Partial pulmonary venous drainage into the right atrium and a posterior atrial septal defect were discovered. Atrio-septo-pexy was performed, at the completion of which the pulmonary veins emptied into the left atrium, and the defect was thought to be closed. Recovery was uneventful.

Comment: As subsequent events have indicated, this patient would probably have been served as well had she been operated upon at normal temperature.

CASE 3.—I. D., a 27-year-old female, had had exercise intolerance for the past year and dyspnea and palpitation for five weeks prior to admission. Catheterization gave evidence of a ventricular septal defect with questionable evidence of an associated atrial septal defect. At exploratory operation under hypothermia, the lowest temperature reached was 26.6° C. (80° F.). One episode of ventricular fibrillation occurred just before surgery was begun. This required immediate thoracotomy. When normal rhythm was re-established it was decided to go ahead with the definitive surgery. An interatrial septal defect was diagnosed and atrio-septo-pexy was performed. During the latter part of the procedure the heart again went into ventricular fibrillation, but following completion of the procedure it was defibrillated and the rhythm was normal. After the chest was closed, ventricular fibrillation again occurred. The chest was reopened, normal rhythm was restored, and the chest was closed. Shortly thereafter, cardiac arrest occurred.

Comment: This patient probably could have been helped by atrio-septo-pexy at normal temperature. The effect of cooling upon her myocardium was detrimental. In spite of the catheterization evidence, no defect of the ventricular septum was found at autopsy.

Four patients had transposition of the great vessels. All were very severely affected.

CASE 4.—E. K., a 6-month-old male, had cyanosis from birth and cardiac failure at 3 months. Angiocardiogram demonstrated transposition. Creation

of an atrial septal communication was decided upon. Under hypothermia (lowest temperature 25.5° C., 78° F.) the cavae were occluded and an atrial communication established. Citrated blood was transfused into the aortic arch during the procedure. Cardiac action was poor following pericardiotomy. Asystole developed some time after completion of the procedure and was treated by manual compression and release of the heart. Ventricular fibrillation responded to continuation of alternate compression and release and normal rhythm was restored. Finally, asystole became permanent, however.

Case 5.—K. C., a male, aged 7 months, was cyanotic from 6 weeks of age. Other symptoms were easy fatigue, dyspnea, and slow weight gain and development. Incomplete cardiac catheterization was performed and a diagnosis was made of pulmonary stenosis with patent foramen ovale. He had a progressive downhill course. At operation on Nov. 10, 1952, under hypothermia (lowest temperature 21.5° C., 71° F.), transposition of the great vessels was found. The cavae were occluded and switch-over anastomosis of the great vessels was performed, after which there was obvious improvement in his condition. Bronchoscopy was carried out for retained secretions approximately thirty hours postoperatively. Cardiac arrest occurred immediately upon insertion of the bronchoscope into the left main bronchus.

Case 6.—G. N., a 3-month-old male, had cyanosis from birth, cough and dyspnea, and poor weight gain. Cardiac failure occurred one week prior to admission. The diagnosis of transposition of the great vessels was made on evidence from fluoroscopy. The course was downhill. At operation under hypothermia (lowest temperature 22.2° C., 72° F.) switch-over anastomosis was performed with the cavae occluded. Following completion of the anastomoses there was slowing of the heart with ultimate asystole.

Case 7.—C. R., a female, aged 10 days, was cyanotic from birth and had a downhill course. A diagnosis of transposition of the great vessels was made on fluoroscopy. Operation was performed at 20° C. (68° F.). The cavae were occluded for twenty-three minutes. Switch-over anastomosis was performed. Slowing of the heart rate was followed by ultimate asystole.

Four patients had the tetralogy of Fallot. All of these, too, were severely affected.

Case 8.—S. G., a female, aged 12 months, was cyanotic from birth. Recently it had increased in degree and was accompanied by dyspnea and marked exercise intolerance. She could not sit up. At the time of admission she was in failure. On fluoroscopy there was evidence of the presence of the tetralogy of Fallot. Under hypothermia, 26.6° C. (80° F.), the infundibular obstruction was removed with modified pituitary forceps. The result was excellent.

Case 9.—In D. L., a female, aged 15 months, cyanosis was first noted at 15 weeks and was progressive. Dyspnea was constant and syncopal episodes were frequent. The diagnosis of the tetralogy of Fallot was confirmed by cardiac catheterization. At operation, hypothermia, 24.4° C. (76° F.), was used and the cavae were occluded four minutes. Resection of the infundibular obstruction was carried out under vision through an incision in the right ventricle. Ventricular fibrillation was followed by death. A coronary air embolism was found at autopsy.

Case 10.—H. M., a 2-year-old male, had been cyanotic since birth and had marked exercise intolerance, dyspnea, and syncope. The diagnosis of the tetralogy of Fallot was confirmed by cardiac catheterization. Under hypothermia (25.5° C., 78° F.), the obstructing infundibular tissue was removed with modified pituitary forceps. The result was excellent.

CASE 11.—In J. C., a 12-month-old male, cyanosis was first noted at 6 months. Other symptoms were dyspnea, exercise intolerance, and loss of weight. Cardiac failure occurred while he was in the hospital. The diagnosis was the tetralogy of Fallot. Hypothermia, 24.4° C. (76° F.), was used at operation. Ventricular fibrillation began when the pericardium was opened. The pulmonary valve area was dilated with sounds. Normal rhythm followed alternate compression and release of the heart but he died several hours later.

Three additional patients had congenital lesions: transposition of the aorta and levoposition of the pulmonary artery with pulmonary stenosis, nonfunctioning right ventricle, and ventricular septal defect.

CASE 12.—B. L., a female, aged 31 months, was cyanotic from birth and had dyspnea, exercise intolerance, and frequent episodes of failure. The diagnosis of transposition of the great vessels or the Taussig-Bing syndrome was made. An exploratory operation with hypothermia, 22.2° C. (72° F.), was performed and the Taussig-Bing syndrome with pulmonary stenosis demonstrated. Pulmonary valvulotomy was performed. The result was excellent.

CASE 13.—D. U., a 3-month-old female, was cyanotic from birth and had developed poorly. An angiocardiogram showed a nonfunctioning right ventricle. Under hypothermia, 24.4° C. (76° F.), the left pulmonary artery was anastomosed to the aorta (end-to-side). She died several hours later. Autopsy showed a nonfunctioning right ventricle and massive hemorrhage in the left lung.

CASE 14.—M. F. was a 15-year-old female. Catheterization provided evidence of a ventricular septal defect. Hypothermia, 24.4° C. (76° F.), was used at operation. The cavae were ligated for six minutes. The right ventricle was opened and the defect was repaired under direct vision by approximation of the edges with sutures. Arterial transfusion into the aortic arch was carried out throughout the period of open intracardiac surgery; 1,000 c.c. of erythrocyte-Ringer-gelatin solution were given followed, inadvertently, by 500 c.c. of citrated blood. Ventricular fibrillation occurred at the termination of definitive surgery. The heart was defibrillated with a single shock. The postoperative course was uneventful. Postoperative catheterization showed that the defect was apparently only partially closed.

The remaining two patients had acquired cardiac lesions: mitral insufficiency in one, aortic insufficiency in the other.

CASE 15.—N. S., a female, aged 31, had advanced mitral insufficiency. Under hypothermia at 25.5° C. (78° F.), commissurotomy and commissurorrhapy were performed. A clot formed in the left atrium during the procedure. Ventricular fibrillation occurred and death ensued.

CASE 16.—T. V., a male, aged 33, had aortic insufficiency with severe symptoms. Under hypothermia, 31.1° C. (88° F.), the patient's blood pressure dropped considerably after exploration of the aortic valve. The left heart was by-passed with an extracorporeal pump. There was considerable blood loss. The pump stopped and the blood pressure was at a critically low level. Resuscitative measures included arterial transfusion of citrated blood. Ventricular fibrillation developed followed by intractable cardiac arrest.

TECHNIQUE OF COOLING

The first two patients subjected to hypothermia (H. D. and J. S., Cases 1 and 2) were cooled in a large food freezer. Hands and feet were wrapped in protective cotton batting and the slatted bottom covered so that no part

of the body would come in contact with a metal surface. An electric fan was placed within the box to keep the cold air circulating. This method was found to be unsatisfactory, the fall in body temperature being very slow.

For the remaining patients a cooling blanket was used,* similar to that employed by Fay many years previously. This consists of a double layer of rubber through which a continuous tube has been coiled. The free ends of the tube outside the blanket afford means for intake and outflow. These are connected to a pump system and any cooling fluid may be circulated through the coil. We have used ice water.

The patient is placed upon the blanket and an endotracheal tube is introduced. Sufficient Pentothal is given to induce narcosis. A slow drip of 0.2 per cent procaine in 5 per cent dextrose solution is used as an adjunct. It is advisable to let the patient breathe 100 per cent oxygen from the beginning. A thermocouple lead is introduced into the rectum, electrocardiograph electrodes are placed, the blanket is closed about the patient, and circulation of the fluid is started. In infants, approximately sixty to ninety minutes are required to lower rectal temperature to 23.3° to 24.4° C. (74° to 76° F.). When the temperature has fallen to a level 2° F. higher than that decided upon before the start of the procedure, the blanket is opened and the patient exposed to room air. Following cessation of cooling, the temperature regularly drops 2°. Further fluctuations of temperature can be controlled by either raising or lowering the temperature of the blanket.

*Available from Thermo-Rite Products Corp., 1748 Main St., Buffalo, N. Y.

OBSERVATIONS DURING COOLING

During the cooling process, several noteworthy events take place. Early, shivering occurs. Inasmuch as this reaction may significantly prolong the time necessary to lower the temperature to the desired level, it must be controlled. This is accomplished with an additional small amount of Pentothal Sodium given intravenously. The electrocardiogram is valuable in the detection of occult shivering. In two infants we found that without any anesthetic agent the temperature fell satisfactorily with no evidence of discomfort or gross shivering.

When a level in the neighborhood of 28° C. (82.4° F.) is reached, spontaneous respiration ceases and the anesthesiologist must assume control. During rewarming, respiration again becomes spontaneous at the same temperature.

The electrocardiogram shows progressive changes. These are in the main comparable to the changes seen in a normal dog cooled over a similar range of temperature. There is prolongation of R-R, P-R, and S-T intervals. In the majority of cases, sinus rhythm is the rule at all temperature levels observed prior to surgery. In the case of N. S. (Case 15) a variety of arrhythmias was observed during cooling. These were, however, in evidence before cooling was started.

The blood pressure usually shows a gradual fall as temperature drops. The pulse rate after an initial acceleration shows a progressive slowing. Usually at 26.7° C. (80° F.) the pulse rate is half the value at 37° C. (98.6° F.).

REWARMING

Immediately following definitive surgery, rewarming is started by cir-

culating warm water through the blanket. Patients cooled below 28° C. (82.4° F.) are rapidly warmed to that temperature. At this level, as noted above, spontaneous respirations again appear. Beyond this point, the temperature is raised slowly. From 31° to 32° C. (87.8° to 89.6° F.) most patients will respond satisfactorily in their own beds with no artificial methods of raising temperature and will attain a normal level in four to twelve hours. Regularly, a rise above normal of 2 to 3° is seen on recovery.

RESULTS

In the series of sixteen patients, the ages ranged from 10 days to 33 years. The temperature at which surgery was performed ranged from 20° to 31.1° C. (68° to 88° F.). A variety of cardiac lesions was operated upon: atrial septal defect, ventricular septal defect, the tetralogy of Fallot, transposition of the great vessels, the Taussig-Bing syndrome with pulmonary stenosis, nonfunctioning right ventricle, mitral insufficiency, and aortic insufficiency.

Eleven patients died (68.7 per cent), eight in the operating room, one at approximately thirty hours, one at twelve hours, one at eight hours. Among those who died were four with transposition (100 per cent), two with the tetralogy of Fallot (50 per cent), one with nonfunctioning right ventricle, two with atrial septal defect (66.6 per cent), and the two patients with acquired heart disease (100 per cent). In these, the temperature reached before operation began embraced the range: 20° to 31.1° C. (68° to 88° F.).

The questions which must be answered in the light of these figures are two: (1) Did hypothermia contribute to the death of any patient? (2) Did hypothermia enhance the chance of survival of any patient? The answers are very difficult to derive and their validity rests too heavily upon that factor denied by the statisticians: medical judgment, which is made of two parts knowledge, one part intuition, and one part hope.

Did hypothermia contribute to the death of any patient? We feel that in all the adult patients who died (Cases 1, 3, 15, and 16), the increased myocardial irritability incident to reduced temperature may have been a factor in the development of ventricular fibrillation. The longer the period of years during which the heart muscle has been subjected to strain, the greater its inability to compensate in stressful situations. In Case 15, hypothermia with consequent slowing of circulation may have been a factor in the production of the large clot which developed in the left atrium.

Did hypothermia enhance the chance of survival of any patient? One's judgment here must be influenced not by the propriety of the operative procedure employed but by its magnitude, not alone by the lesion treated but by the patient's condition. Bearing these two criteria in mind, an affirmative answer to the question must be given. E. K. (Case 4) was, and had been, in a very precarious state. It appears extremely unlikely that at normal body temperature he would have survived even thoracotomy. His cardiac action, however, at 25.5° C. (78° F.) persisted through five minutes of interruption of the circulation and for forty minutes thereafter. We believe that failure of the circulation was due to acute overload of the right heart, the septal communication having been

made too large. The use of citrated blood during the period of caval occlusion may have been an important contributory cause.

K. C. (Case 5) had been diagnosed as having pulmonary stenosis with patent foramen ovale. When transposition of the great vessels was discovered, the pediatric cardiologist and the surgeon agreed that all was lost unless rerouting of the circulation could be speedily accomplished. It was agreed that a radical procedure was justified, what we have termed a switch-over anastomosis of the great vessels. This operation had been discussed in many previous conversations and had been discarded as a possible solution to the problem. However, in desperation it was performed. It must be granted that under ordinary circumstances of body temperature, interruption of the circulation for twenty-two minutes would not have been possible. This infant actually was improved postoperatively, and it was by what we choose to believe an accident unassociated with the surgery that his death was brought about.

G. N. and C. R. (Cases 6 and 7) also had transposition of the great vessels and were subjected to the same procedure. Again, the circulation was interrupted for a period of time which would not have been possible at normal body temperature.

S. G., H. M., and B. L. (Cases 8, 10, and 12), were considered to have only a very slight chance of surviving operation. The reduced tissue demand for oxygen under hypothermia was certainly a big factor in the happy outcome.

D. L., J. C., and D. U. (Cases 9, 11, and 13) also were considered to be extremely poor risks. The procedures employed would, we feel certain, have resulted in death more quickly at normal temperature.

INDICATIONS AND CONTRAINDICATIONS

Tentative conclusions in regard to indications and contraindications for the use of hypothermia may be drawn from this small series of patients. As more is learned of this modality, changes will undoubtedly be made.

At present we believe that hypothermia is indicated as part of the anesthetic regimen in all severely cyanotic and disabled infants who are to undergo cardiac surgery of any nature. The optimum range of temperature is probably 23.3° to 26.1° C. (74° to 79° F.).

The presence of moderate cyanosis and disability in infants and children who are to undergo such time-consuming procedures as Blalock or Potts anastomosis, transposition of pulmonary veins, etc., would indicate the production of low body temperature during surgery as a means of decreasing oxygen demand. The level in these cases may be higher, but probably should be near 31.1° C. (88° F.).

If it is the surgeon's intention to open a cardiac chamber or to interrupt the circulation during the performance of an operation, hypothermia is certainly indicated. An effective and reliable heart-lung apparatus might be a better answer to the problem involved here, but until it is perfected, hypothermia best fills the need. Intra-arterial transfusion is a necessary adjunct.

The chief contraindication to the use of hypothermia is the presence of a noncyanotic lesion for which the surgical technique does not require

interruption of the circulation. Atrio-septo-pexy, mitral or aortic commissurotomy, and mitral commissurorrhaphy are examples. There is probably an inherent factor in acquired lesions which contraindicates the production of low body temperature, and that is myocardial damage. Arrhythmias are more prone to develop.

Advanced age is also a contraindication. Ideal in infants and young children, hypothermia should be used cautiously in older children and should be avoided in those over the age of 10 years.

REFERENCES

1. Fay, T., and Henny, G. C.: Correlation of Body Segmental Temperature and Its Relation to the Location of Carcinomatous Metastasis. Clinical Observations and Response to Methods of Refrigeration, Surg., Gynec. & Obst. **66**: 512, 1938.
2. Smith, L. W., and Fay, T.: Temperature Factors in Cancer and Embryonal Cell Growth, J. A. M. A. **113**: 653, 1939.
3. Smith, L. W., and Fay, T.: Observations on Human Beings With Cancer, Maintained at Reduced Temperature of 75° to 90° Fahrenheit (Refrigeration), Am. J. Clin. Path. **10**: 1, 1940.
4. Fay, T., and McCravey, A.: Pain Relief by Local and Generalized Refrigeration, Dis. Nerv. Syst. **1**: 209, 1940.
5. Fay, T.: Prolonged Human Refrigeration, New York J. Med. **40**: 1351, 1940.
6. Fay, T., and Smith, G. W.: Observations on Reflex Responses During Prolonged Periods of Human Refrigeration, Arch. Neurol. & Psychiat. **45**: 215, 1941.
7. Talbott, J. H.: The Physiologic and Therapeutic Effects of Hypothermia, New England J. Med. **224**: 281, 1941.
8. Talbott, J. H.: The Effect of Cold. In Oxford Medicine IV, Part 3, 664 ff.
9. Talbott, J. H.: Hypothermia. In Cold Injury, New York, 1952, Josiah Macy, Jr. Foundation, 145 ff.
10. McQuiston, W. O.: Anesthetic Problems in Cardiac Surgery in Children, Anesthesiology **10**: 590, 1949.
11. McQuiston, W. O.: Anesthesia in Cardiac Surgery. Observations on Three Hundred and Sixty-two Cases, Arch. Surg. **61**: 892, 1950.
12. Bigler, J. A., and McQuiston, W. O.: Body Temperatures During Anesthesia in Infants and Children, J. A. M. A. **146**: 551, 1951.
13. Bigelow, W. G., Lindsey, W. K., Harrison, R. C., Gordon, R. A., and Greenwood, W. F.: Oxygen Transport and Utilization in Dogs at Low Temperatures, Am. J. Physiol. **160**: 125, 1950.
14. Bigelow, W. G., Callaghan, J. C., and Hopps, J. A.: General Hypothermia for Experimental Intracardiac Surgery. The Use of Electrophrenic Respirations, an Artificial Pacemaker for Cardiac Standstill, and Radio-frequency Rewarming in General Hypothermia, Ann. Surg. **132**: 531, 1950.
15. Bigelow, W. G., Lindsey, W. K., and Greenwood, W. F.: Hypothermia, Its Possible Role in Cardiac Surgery: An Investigation of Factors Governing Survival in Dogs at Low Body Temperatures, Ann. Surg. **132**: 849, 1950.
16. Cookson, B. A., Neptune, W. B., and Bailey, C. P.: Hypothermia as a Means of Performing Intracardiac Surgery Under Direct Vision, Dis. Chest **22**: 245, 1952.
17. Downing, D. F., Cookson, B. A., Goldberg, H., Weller, R., and Imbriglia, J.: Follow-up Studies on Dogs Subjected to Hypothermia. To be published.
18. Cookson, B. A., and DiPalma, J.: The Use of WIN 2173 for the Correction of Bradycardia Occurring in Severe Hypothermia. To be published.
19. Cookson, B. A., and Costas-Durieux, J.: The Creation and Closure of Atrial Septal Defects in Dogs. Use of Arterial Transfusion. To be published.
20. Cookson, B. A., Costas-Durieus, J, and Bailey, C. P.: The Risk of Citrated Blood for Intra-arterial Transfusion. To be published.
21. Neptune, W. B., Cookson, B. A., Bailey, C. P., Appler, R., and Rajkowski, F.: Complete Homologous Heart Transplantation. A. M. A. Arch. Surg. **66**: 174, 1953.
22. Bailey, C. P., Downing, D. F., Geckeler, G. D., Likoff, G., Goldberg, H., Scott, J. C., Janton, O., and Redondo-Ramirez, H. P., Congenital Interatrial Communications: Clinical and Surgical Considerations With a Description of a New Surgical Technic: Atrio-septo-pexy, Ann. Int. Med. **37**: 888, 1952.

THE TOTAL CIRCULATING EOSINOPHIL COUNT UNDER ENVIRONMENTAL AND STRESS STIMULI

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HISTORY

SINCE Ehrlich first accurately described the eosinophilic leukocyte well over a century ago, a large amount of experimental work has been done in an attempt to explain the role of this cell. Nonetheless, certain aspects of the significance of the eosinophil cell have lacked recognition in clinical medicine until the recent revival of interest initiated by Dalton and Selye,[1] Thorn and associates,[2] Laragh and Almy,[3] Recant and co-workers[4] and others, who demonstrated the role of this cell in the alarm reaction, and its usefulness in assessing the integrity of the pituitary-adrenal system.

The presence of eosinophilia has long had an obvious and generally recognized association with such conditions as helminth infestation, allergy, certain dermatoses, malignancies, and postinfectious states. Eosinopenia, on the other hand, although first noted by Ehrlich in infectious states, has been largely overlooked as a significant finding. This was partly due to the technical difficulties of doing accurate eosinophil counts. The earlier method of reporting the cell count as a percentage of the total leukocyte count proved inaccurate and misleading. The total eosinophil count, expressed as an absolute figure, has proved more satisfactory although there are in use many variations in technique of counting and staining.

From the Research Foundation, Children's Hospital.

Despite the fact that eosinopenia was found to occur in almost every infectious disease, the phenomenon was usually interpreted as being a specific response to a particular disease entity. Similarly, the post-toxic eosinophilia was considered a specific effect; for example, it was considered as diagnostically significant in scarlet fever[5, 6] and infectious mononucleosis.[7] It was not until the last decade that eosinopenia, with counts falling even to zero, was recognized as being a nonspecific response to any acute infection which was usually followed by a postinfectious eosinophilia.

The degree of the fall, as well as of the subsequent rise of the total eosinophil count, was recognized as correlating with the severity of the illness in the acute and convalescent phase, and in this respect was considered to be a useful prognostic laboratory test. Many attempts were made to correlate this phenomenon with the leukocyte count, degree of fever, sedimentation rate, and with specific therapy used. However, no good correlation was found to exist other than with the actual clinical appearance of the patient.[8, 9]

The fall of the eosinophil count following trauma was recognized long before Selye described his "alarm reaction." In 1893, Zappert demonstrated a fall in eosinophils after tuberculin injections. Eosinopenia has since been demonstrated following convulsions, intravenous injections, and surgical

procedures and is a generally accepted prognostic indicator in postoperative patients.[10, 11, 12]

In 1936, Selye[13] described his well-known "alarm reaction" or general adaptation syndrome. This concept holds that stress stimulates the production of the glucocorticoids by the adrenal gland, which in turn stimulates gluconeogenesis, thymic and lymphatic involution and neutrophilia, lymphopenia and eosinopenia. In 1948 Hills and associates[14] presented evidence that ACTH produced eosinopenia by adrenal stimulation. Epinephrine was later found to produce a similar response presumably by its action on the pituitary-adrenocortical system, and the two drugs, ACTH and epinephrine, soon came into popular usage as a test of the integrity of the pituitary-adrenal axis.[2, 3, 4] Recent experience with the epinephrine test, however, seems to indicate that it may not assess the functional capacity of these organs accurately.[15, 16]

That an acute infection constitutes a stress factor producing eosinopenia seems indisputable. What the actual function of the eosinophil cell is, whether it is in some way related to the immune process, and in what manner it so dramatically and mysteriously disappears from the blood stream are unanswered questions which have precipitated an intensive amount of investigation.

REVIEW OF PEDIATRIC LITERATURE

The literature contains a paucity of information regarding the eosinophil response in the pediatric age group. The consensus at the time of Finn Rud's summary[17] was that the relative eosinophil count had a range of from 0 to 7 per cent in infants, 2 to 5 per cent in preschool and school children, and a drop to an average of 3 per cent at ages 13 to 15 years.

Burrell[18] studied seventy-five premature infants. She found zero or near zero levels in the total eosinophil count for all premature infants on the first day of life (those weighing less than 4½ pounds having consistently zero counts). During the first two days of life, eosinophil counts in almost all cases were extremely low. Where the progress of the infant was entirely satisfactory, the eosinophil count steadily rose to reach a high level by the third to the fifth week at which time it ranged from 900 to 1,650. Of eight infants who died, there was no tendency for the count to rise and zero counts were present at death. This might be construed as being of prognostic importance. Sixty-three infants had counts from 376 to 1,650 which was well above the absolute count for adults of 150 to 400. Discombe[19] found that only 1 per cent of normal adults had a count exceeding 240.

Jailer and co-workers[20] were particularly interested in the pituitary-adrenal relationship in forty-two newborn and twenty-three premature infants. They found an initial count varying from 20 to 537. There was no significant tendency toward a rise or fall in twelve full-term infants in the first week of life. Two-thirds of the full-term infants responded to the epinephrine test in the first two days. None of the prematures responded until the ninth day, and the smaller the birth weight, the longer it took for the epinephrine test to become positive. All infants in this series responded to ACTH. They conclude that in premature infants the mechanism for ad-

justment to stress is not completely developed at birth.

Klein and Hanson,[21] also studying adrenocortical function in the newborn infant, found in thirty infants an average count of 370 with a small decrease at one week. They noted much less response to ACTH in infants in the first week of life than in the second week.

Medoff and Barbero[22] found a range of 19 to 851 (mean 267) in forty-two full-term newborn infants. In 75 per cent of the infants, the count rose significantly during the first five days of life, and in 82 per cent a significant rise occurred from 5 to 30 days of age, with a range of 69 to 571 and a mean of 248. In contrast, the mothers of these infants showed an abrupt rise to a fixed level in forty-eight to seventy-two hours. On the basis of these counts they postulated a period of relative hypoadrenalism in infants from 5 to 60 days of age.

In Hain's study,[23] variations among age groups are not stressed. She found that eighteen healthy children had eosinophil counts within the normal adult range. Twelve patients with nonfebrile chronic illnesses also were normal which would seem to indicate adaptation to chronic stress. In twenty-nine patients with acute febrile illnesses, she found an eosinopenia of zero to 97, with a subsequent rise paralleling recovery. In twenty-three patients (including normal, active, and inactive rheumatic fever, and miscellaneous nonfebrile illnesses) Hain found a normal adult response to the Thorn test.

PRESENT STUDY

In the course of clinical studies, we have frequently observed marked eosinopenia (zero or near-zero levels) occurring in the acute phase of infection and a subsequent post-toxic eosinophilia. On several occasions in patients with acute pyogenic meningitis, a fall in the eosinophil count during the convalescent phase has presaged by one or more days the recognition of a complication or relapse. In view of these observations, it appeared to be of some importance to determine to what extent a daily eosinophil count might vary as a result of procedures and conditions inherent in the treatment of a disease such as meningitis. If a significant variation occurs in the pediatric age group, for example, after fasting, intramuscular injections, lumbar punctures, and other noxious stimuli, a daily eosinophil count would be invalid as a prognostic sign unless the daily counts were performed under rather rigidly controlled conditions. With this in mind, the present study was set up using several different age groups and taking sample eosinophil counts under controlled and simulated conditions of stress.

Methods and Materials.—Nineteen patients were studied. Of these, four ranging in age from 8 to 12 years were postpoliomyelitis patients hospitalized for orthopedic rehabilitation. An additional four patients ranging in age from 1 to 2 years were also postpoliomyelitis patients. Eleven infants, aged 2 to 12 months, were convalescent diarrhea patients.

The method of performing total eosinophil counts was that of Thorn, using the Randolph modification. All counts were done by the same technician.

Eosinophil counts were done simultaneously on all of the patients in a given age group under study. Other

than for physical therapy in the postpoliomyelitis group, none of the patients was receiving medication or other specific treatment.

Results.—Fasting eosinophil counts in the nineteen patients studied ranged from 50 to 470, with 80 per cent of the patients having counts in the range of 50 to 300. There was a variation of only 10 cells among individuals in the older age group and 50 in the 1- to 2-year group. The widest variation occurred among patients under 1 year. (Table I.)

TABLE I. FASTING EOSINOPHIL COUNTS. AGE VARIATION

8-12 YR.	1-2 YR.	6-12 MO.	2-6 MO.
90	90	150	50
90	110	100	50
90	130	170	90
100	140	330	100
		730	220
			470

Fasting counts done on three consecutive days on three patients in the 2- to 6-month group showed a fluctuation of 30, 30, and 80 in successive counts. (Table II.)

TABLE II. DAILY FASTING EOSINOPHIL COUNTS. VARIATION IN 2 TO 6 MO. AGE GROUP

1ST DAY	2ND DAY	3RD DAY
50	130	110
90	70	100
50	20	20

Effect of Food Ingestion.—To determine the effect of food ingestion upon the circulating eosinophil level, counts were done before breakfast, thirty minutes and two hours after breakfast, and two hours after lunch. (Table III.) Eosinophil counts done thirty minutes after breakfast ranged from 40 to 790 with 90 per cent of the patients' counts in the range of 50 to 300. Again, the counts were most uniform in the oldest age group while the widest range occurred in the 2- to 12-month group. There was no consistent trend in the postprandial counts since 50 per cent rose or remained the same while 50 per cent fell. The actual degree of rise or fall in which the postprandial counts differed from those taken before meals varied from 100 to 660 with 90 per cent differing less than 200.

TABLE III. THE EFFECT OF FOOD INGESTION UPON TOTAL EOSINOPHIL COUNTS

AGE GROUP	FASTING	30 MIN. P.C. (BREAKFAST)	2 HR. P.C. (BREAKFAST)	2 HR. P.C. (LUNCH)
8-12 yr.	90	100	50	120
	100	180	200	350
	90	190	210	300
	90	160	180	130
1-2 yr.	130	110	80	130
	140	140	200	440
	110	190	190	150
	90	60	110	80
6-12 mo.	100	60	100	50
	170	110	80	160
	730	790	350	700
	330	160	130	140
	150	60	70	60
2-6 mo.	50	60	10	20
	90	110	160	90
	220	120	230	240
	50	40	20	10
	470	70	730	510

Effect of Diurnal Variation.—The occurrence of a diurnal variation in total eosinophil counts in adults has been established by others.[17, 24] In the patients under study, 4 P.M. counts ranged from 20 to 630. Only 50 per cent of these counts, as compared with 80 per cent of fasting counts done on the same day, fell within a range of 50 to 300. In eighteen patients the afternoon counts rose in seven and fell in eleven. With one exception 4 P.M. counts, as compared with fasting

counts, rose in the two older age groups and fell in the younger. Four P.M. counts done on three consecutive days on three patients in the 2- to 6-month age group showed a fluctuation of 40, 40, and 70 in successive counts. This daily fluctuation closely corresponds with that found in fasting counts. (Table IV.)

TABLE IV. COMPARISON OF FASTING WITH 4 P.M. EOSINOPHIL COUNTS

AGE GROUP	FASTING—A.M.	4 P.M.
8-12 yr.	90	130
	100	220
	90	430
	90	380
1-2 yr.	130	170
	140	190
	110	170
	90	30
6-12 mo.	100	20
	170	90
	730	630
	150	70
2-6 mo.	100	40
	50	40
	90	50
	220	180
	50	40
	470	300

Effect of Traumatic Stimuli.—In order to determine the effect of traumatic stimuli such as intramuscular injections, two successive placebos were administered into the gluteal muscles of patients in the 8- to 12-year and 1- to 2-year age groups. The 8- to 12-year group showed a consistent fall, reflected in counts done fifteen and thirty minutes after the injection but not in those done three hours later. The fall ranged from 10 to 70. There was no consistent response in the 1- to 2-year age group. (Table V.)

Lumbar punctures performed in three patients in the 2- to 12-month age group similarly showed a fall in counts done fifteen and thirty minutes later. The decrease in eosinophils ranged from 50 to 90. Two hours later the counts had returned to their previous levels. (Table VI.)

TABLE V. THE EFFECT OF INTRAMUSCULAR INJECTIONS ON EOSINOPHIL COUNTS

AGE GROUP	BEFORE	15 MIN. AFTER	30 MIN. AFTER	3 HR. AFTER
		A.M. Injection		
8-12 yr.	80	70	50	220
	190	160	120	300
	190	190	150	160
	200	140	130	70
1-2 yr.	130			100
	220	150	240	200
	110	140	120	210
	50	60	50	20
		P.M. Injection		
8-12 yr.	100	60	80	60
	180	300	200	300
	180	120	190	70
	120	50	140	80
1-2 yr.	230	90	90	140
	200	230	190	230
	140	180	160	190
	30	50	50	150

TABLE VI. THE EFFECT OF LUMBAR PUNCTURE ON EOSINOPHIL COUNTS

BEFORE	15 MIN. AFTER	30 MIN. AFTER	2 HR. AFTER
170	80	70	170
90	40	90	120
220	140	140	170

Effect of Intravenous Infusions.—Continuous intravenous infusions were given to three patients in the 2- to 6-month age group. The infusion fluid consisted of 5 per cent glucose in water for the first three hours, and protein hydrolysate* for the second three hours. The infusion ran at 8 to 10

TABLE VII. THE EFFECT OF INTRAVENOUS INFUSIONS ON EOSINOPHIL COUNTS

BEFORE INFUSION	5% GLUCOSE IN WATER			PROTEIN HYDROLYSATE		
	1 HR.	2 HR.	3 HR.	1 HR.	2 HR.	3 HR.
30	0	10	50	10	20	20
140	100	110	110	80	110	100
110	70	200	260	150	190	110

*Travamin.

drops per minute. Hourly counts following the initiation of 5 per cent glucose in water showed a fall of 30 to 40 eosinophils in the first hour. This slowly rose to approximately the initial level in three hours. However, on changing the solution to protein hydrolysate there occurred a second fall of 40 to 100, which again gradually rose in the ensuing three hours. (Table VII.)

DISCUSSION

With two exceptions, all fasting eosinophil counts were within the range of normal of 80 to 500 given by Roche and associates.[25] Fasting counts done in the oldest age group showed the least individual variation, while those in the youngest group varied widely.

No consistent postprandial effect was observed in the present study. Finn Rud[17] similarly found that meals had no effect on the total count in adults.

No consistent diurnal trend was noted in our patients. An afternoon rise occurred in the oldest age group and a fall in the youngest. Four P.M. counts showed a wider range in members of all age groups than did fasting counts done on the same day. These counts did not encompass the period between 4 P.M. and 9 A.M. Finn Rud[17] reported a decrease in eosinophils in early morning with a minimum between 9 and 11 A.M. This is followed by a brief increase at noon with the highest values occurring in the late afternoon after 5 P.M.

Traumatic procedures, such as intramuscular injections and lumbar punctures, resulted in a brief sustained fall in total eosinophil counts of as much as 100 in the majority of patients in this study.

There have been several reports of an eosinopenia following glucose administration.[4, 11, 26] Whether this effect is a specific adrenal stimulus or a nonspecific stress stimulus is not known. In three patients receiving continuous intravenous infusions, a drop in the eosinophil count followed by a slow rise occurred after both 5 per cent glucose and protein hydrolysate were started.

There are many other reports of eosinopenia following therapeutic procedures, e.g., electroshock therapy, insulin, and electrically induced convulsions,[10] nitrogen-mustard therapy, insulin, sedation (intoxicating doses), cardiazol injections,[17] and sodium salicylate therapy.[27] Other factors reported as altering the eosinophil response include starvation,[17] malnutrition, hypoproteinemia,[28] vitamin C administration, and DOCA or salt administration over prolonged periods.[29] The number of uninvestigated specific and nonspecific stress factors altering the eosinophil response probably are considerable.

In addition, Finn Rud[17] has demonstrated that the eosinophil system in the peripheral blood is in contant oscillating motion about a mean value. He found that the extreme variation in ten counts per patient done at one- and five-minute intervals ranged between 263 and 631 in ninety patients studied. This represents a significant variation over and above that found in successive counts of the same sample.[15]

When one appreciates the wide range of stimuli which may affect the total eosinophil count, it seems remarkable that daily counts could reflect any consistent trend paralleling

clinical recovery. That they do is undisputable. However, it would appear necessary that daily counts be drawn under as rigidly controlled conditions as possible in order to eliminate extraneous stimuli. From the present study, it would appear that fasting counts are the least subject to variation.

CONCLUSIONS

1. A review of the literature regarding the total circulating eosinophil count is presented with particular reference to studies done in the pediatric age group.

2. From the present study of nineteen pediatric patients, in which sample total eosinophil counts were done under controlled and simulated conditions of stress, the following conclusions are drawn:

a. Fasting eosinophil counts were within the normal range of 80 to 500. They also appeared to be the least variable of counts done at varying intervals throughout the day.

b. No consistent postprandial effect was found.

c. No consistent diurnal trend was noted.

d. Traumatic procedures, such as intramuscular injections and lumbar punctures, produced a brief unsustained fall in eosinophil count.

e. The administration of intravenous fluids such as 5 per cent glucose and protein hydrolysate produced a brief fall followed by a sustained rise in eosinophil count.

3. When daily eosinophil counts are to be done, it is recommended that a fasting count be performed since it is the least subject to variation.

REFERENCES

1. Dalton, A. J., and Selye, H.: The General Adaptation Syndrome and the Diseases of Adaptation, J. Clin. Endocrinol. **6**: 117, 1946.
2. Thorn, G. W., Forsham, P. H., Prunty, F. T. G., and Hills, A. G.: A Test for Adrenal Cortical Insufficiency, J. A. M. A. **137**: 1005, 1948.
3. Laragh, J. H., and Almy, T. P.: Changes in Circulating Eosinophils in Man Following Epinephrine, Insulin and Surgical Operations, Proc. Soc. Exper. Biol. & Med. **69**: 499, 1948.
4. Recant, L., Hume, D. M., Forsham, P. H., and Thorn, G. W.: Studies on the Effect of Epinephrine on the Pituitary-adrenocortical System, J. Clin. Endocrinol. **10**: 187, 1950.
5. Friedman, S.: Eosinophilia in Scarlet Fever as a Diagnostic Aid, Am. J. Dis. Child. **49**: 933, 1935.
6. Bowie, J. M.: The Leukocytosis in Scarlet Fever and Its Complications, J. Path. & Bact. **8**: 82, 1903.
7. Kauffman, R. E.: Eosinophilia in Infectious Mononucleosis, Am. J. M. Sc. **219**: 206, 1950.
8. Weiner, H. A., and Morkovin, D.: Circulating Blood Eosinophils in Acute Infectious Disease and the Eosinopenic Response, Am. J. Med. **13**: 58, 1952.
9. Lowell, F. C., and Wellington, M. S.: The Eosinophil Count in Acute Infections, Bull. New England Med. Center **7**: 440, 1949.
10. Altschule, M. D., Parkhurst, B. H., and Tilletson, K. J.: Decreases in Blood Eosinophilic Leukocytes After Electrically Induced Convulsions in Man, J. Clin. Endocrinol. **9**: 440, 1949.
11. Jordan, P. H., Last, J. H., Pitesky, I., and Bond, E.: Eosinopenia due to Glucose Administration, Proc. Soc. Exper. Biol. & Med. **73**: 243, 1950.
12. Coppinger, W. R., and Goldner, M. G.: The Eosinophil Response to Surgical Trauma, Surgery **28**: 75, 1950.
13. Selye, H.: A Syndrome Produced by Diverse Nocuous Agents, Nature **138**: 32, 1936.
14. Hills, A. G., Forsham, P. H., and Finch, C. A.: Changes in Circulating Leukocytes Induced by the Administration of Pituitary Adrenocorticotrophic Hormone (ACTH) in Man, Blood **3**: 755, 1948.
15. Best, W. R., Kark, R. M., Muehrcke, R. C., and Samter, M.: Clinical Value of Eosinophil Counts and Eosinophil Response Tests, J. A. M. A. **151**: 702, 1953.
16. Thorn, G. W., Jenkins, D., Laidlaw, J. C., Goetz, F. C., Dingman, J. F., Arons, W. L., Streeton, D. H., and McCracken, B. H.: Pharmacologic Aspects of Adrenocortical Steroids and ACTH in Man, New England J. Med. **248**: 588, 1953.

17. Rud, F.: The Eosinophil Count in Health and in Mental Disease; a Biometrical Study, Acta psychiat. et neurol., Supp. 40, 1947.
18. Burrell, J. M.: A Comparative Study of the Circulating Eosinophil Level in Babies. Part I: Premature Infants, Arch. Dis. Child. 27: 134, 1952.
19. Discombe, G.: Criteria of Eosinophilia, Lancet 1: 195, 1946.
20. Jailer, J. W., Wong, A. S., and Engle, E. T.: Pituitary Adrenal Relationship in Full-term and in Premature Infants, as Evidenced by Eosinophil Response, J. Clin. Endocrinol. 11: 1, 1951.
21. Klein, R., and Hanson, J.: Adrenocortical Function in the Newborn Infant as Measured by Adrenocorticotropic Hormone-Eosinophil Response, Pediatrics 6: 192, 1950.
22. Medoff, H. S., and Barbero, G. J.: Total Blood Eosinophil Counts in the Newborn Period, Pediatrics 6: 737, 1950.
23. Hain, K.: Circulating Eosinophils in Children in Health and Disease, Pediatrics 7: 408, 1951.
24. Halberg, F., Visscher, M. B., Flink, E. B., Berge, K., and Bock, F.: Diurnal Rhythmic Changes in Blood Eosinophil Levels in Health and in Certain Diseases, Journal-Lancet 71: 8, 1951.
25. Roche, M., Hills, A. G., and Thorn, G. W.: Levels of Circulating Eosinophils and Their Response to ACTH in Surgery: Their Use as an Index of Adrenal Cortical Function, Proc. of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, 1950, The Blakiston Co.
26. Artunkal, S., and Kayahan, S.: The Effect of Glucose on the Circulating Eosinophils, J. Clin. Endocrinol. & Metab. 12: 1095, 1952.
27. Roskam, J., Van Cauwenberge, H., and Mutser, A.: Effect of Sodium Salicylates on Circulating Eosinophils and Urinary Uric Acid-Creatinine Ratio, Lancet 2: 9, 1951.
28. Brenner, L. O., Waife, S. O., and Wohl, M. G.: The Eosinophil Response in Chronic Disease and Malnutrition, J. Lab. & Clin. Med. 37: 593, 1951.
29. Bonner, C. D., and Homburger, F.: Some Factors Altering the Level of Circulating Eosinophils, Bull. New England Med. Center 13: 187, 1951.

STUDIES OF 17-HYDROXYCORTICOSTEROIDS

III. Blood Levels in Salicylate Intoxication

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THERE has been considerable evidence to suggest that salicylates may, in high doses, influence the pituitary-adrenal system and its secretions. Salicylates have been reported to produce an eosinopenia,[1-4] a depletion of adrenal ascorbic acid and cholesterol,[5-9] and histologic indications of adrenal activation.[6, 10] Alterations in the rate of urinary excretion of steroids[11, 12] and certain metabolic changes similar to those produced by ACTH and cortisone[1, 13, 14] have been noted to follow salicylate administration. In an earlier communication,[15] a markedly elevated plasma 17-hydroxycorticosteroid concentration was reported in one child with salicylate intoxication. Additional subjects with salicylate intoxication have been studied. The purpose of this communication is to report data concerning the plasma 17-hydroxycorticosteroid concentrations observed in these individuals as well as those observed in guinea pigs given large doses of salicylate.

MATERIALS AND METHODS

The human subjects used in this study included three children and four adults with salicylate intoxication. Blood specimens were collected in heparinized syringes from antecubital or external jugular veins. Following the removal of aliquots for salicylate, pH, and other blood chemistry determinations, plasma was separated by centrifugation and stored in a deep freezer until used.

In the animal experiments, male guinea pigs weighing 450 to 600 grams were used. Each animal, except those of a control group, was given a 1 ml. intraperitoneal injection containing the dose of drug indicated in Table III. All solutions injected were at a temperature of 37° C. Blood specimens were obtained from the abdominal aortas. Animals given 75 mg. of sodium salicylate were divided into four groups and individual groups were sacrificed at intervals of two, four, eight, and twenty-four hours following injection. Animals of other treatment groups were sacrificed four hours after the administration of test doses. Plasmas were separated by centrifugation and stored in a deep freezer until used.

17-Hydroxycorticosteroid plasma concentrations were measured by the method of Nelson and Samuels.[16] Plasma salicylate determinations were by the method of Brodie and associates.[17] Plasma pH was determined electrometrically.

OBSERVATIONS

In Table I are shown the data obtained concerning seven patients with

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salicylate intoxication. Case histories are briefly as follows:

R. W., male, aged 9 months. For five days prior to admission, the patient's parents had been giving him 5 grain aspirin tablets, as many as six per day, for a mild pharyngitis. One day prior to admission he developed dizziness, malaise, and hyperpnea. At the time of admission, the temperature was 101° F.; pulse, 100; respirations, 40 and of Kussmaul type. Urine pH was 5.0; urine positive for diacetic acid, acetone and salicylate; plasma CO_2, 8.7 mM per liter; pH, 7.31; plasma salicylates, 33 mg. per cent. He was treated with oral fluids, which included sodium lactate solution. The following day, plasma CO_2 was 15.4 mM per liter; pH, 7.46; the urine was negative for acetone, diacetic acid, and salicylates. One day after admission a blood sample was obtained for study (Table I). Treatment with oral fluids resulted in complete recovery.

K. S., female, aged 29 months. Twenty-three hours prior to admission, she ingested fifteen to twenty aspirin tablets, 1¼ grain size. No vomiting followed. Twelve hours later she was noted to be drowsy, perspiring excessively, and breathing "heavily." Upon admission, the temperature was 99.6° F.; pulse, 110; respirations were deep and at the rate of 32 per minute. She was alternately alert and lethargic. The urine had a pH of 5.0 and gave a strongly positive ferric chloride test. A blood sample was obtained for study (Table I) prior to the start of therapy. CO_2 was 16 mM per liter; pH, 7.26; plasma salicylates, 32 mg. per cent; chlorides, 103.5 meq. per liter. Treatment with oral fluids resulted in complete recovery.

A. G., male, aged 29 months. Twenty-four hours prior to admission, the patient ingested ten to twenty 5 grain aspirin tablets. Three hours later he began vomiting and continued to vomit intermittently over a ten-hour period. He was admitted to another hospital after becoming comatose. The temperature was 101.2° F.; pulse, 120; respirations, 46 at the time of admission. He was given 200 ml. of whole blood and 2,100 ml. of intravenous fluids which included sodium lactate, dextrose in saline, and Ringer's lactate solutions. The following day his temperature was 101.4° F.; pulse, 112; respirations, 40. A blood sample was obtained at this time (forty-eight hours after aspirin ingestion and twenty-four hours after start of therapy); the plasma salicylates were 21.5 mg. per cent. The data are shown in Table I.

D. G., male, aged 16 years. The patient claimed to have ingested 100 5 grain aspirin tablets and twenty "Anacin" tablets (contain acetophenetidin, aspirin, and caffein) in a suicide attempt, eighteen hours prior to admission. Four to five hours after

TABLE I. PLASMA 17-HYDROXYCORTICOSTEROID CONCENTRATIONS IN PATIENTS WITH SALICYLATE INTOXICATION

PATIENT	AGE	DURATION INTOXICATION	PLASMA SALICYLATE (MG./100 ML.)	PLASMA pH	PLASMA 17-HYDROXY-CORTICOSTEROIDS (μG/100 ML.)
R. W.	9 mo.	4 da.	33	7.46	44.0
K. S.	29 mo.	24 hr.	32	7.26	48.2
A. G.	29 mo.	48 hr.	22		41.0
D. G.	16 yr.	16 hr.	64	7.44	31.4
		38 hr.	19	7.48	7.3
S. B.	17 yr.	4 hr.	60		30.5
J. G.	21 yr.	2½ hr.	35	7.47	43.7
C. A.	61 yr.	14 hr.	51	7.51	33.4
		38 hr.	28		20.5

ingestion of the salicylates he noted mild vertigo and mental confusion, and during the ensuing eight hours vomited three or four times. At the time of admission, the temperature was 97.2° F.; pulse, 96; respirations were deep and at the rate of 28 per minute. His face was plethoric, and he complained of tinnitus and nausea. A blood specimen was obtained for study (Table I) prior to the start of therapy. Plasma CO_2 was 19.3 mM per liter, pH, 7.44; plasma salicylates, 64 mg. per cent. During the twenty-four hours following admission, he received 1,000 ml. of intravenous fluids, which included sodium lactate and dextrose in saline solutions, and 2,000 ml. of oral fluids. At the end of this period (thirty-eight hours after salicylate ingestion and twenty-four hours after start of therapy) a second blood specimen was obtained for study (Table I). At that time, plasma CO_2 was 26.9 mM per liter; pH, 7.48; plasma salicylates, 19 mg. per cent. The patient was alert throughout his hospital stay and recovered completely.

S. B., female, aged 17 years. The patient claimed to have ingested 100 5 grain aspirin tablets in a suicide attempt, two and one-half hours prior to her appearance at the emergency room. Upon admission she was plethoric, mildly ataxic, and complained of tinnitus and difficulty in hearing. She had not vomited. Gastric lavage was performed. A blood specimen was obtained for study approximately four hours after aspirin ingestion (Table I). Plasma salicylates were 60 mg. per cent. The patient recovered completely with no therapy.

J. G., female, aged 21 years. Two and one-half hours prior to admission the patient ingested twenty to thirty "Bufferin" tablets (each tablet contains 5 grains aspirin plus gastric antacids), eighteen "Anacin" tablets, and approximately twelve Aureomycin capsules in a suicide attempt. A blood specimen was obtained immediately upon admission to the hospital emergency room (data in Table I). The plasma pH was 7.47; plasma salicylates, 35 mg. per cent. At that time the patient was vomiting repeatedly and was moderately disoriented, but was not stuporous. Gastric lavage was performed, and the patient recovered without further therapy.

C. A., female, aged 61 years. Eighteen hours prior to admission the patient began taking two 5 grain aspirin tablets every half hour to relieve pain following removal of a bunion. She continued to ingest aspirin at this rate for approximately ten hours, during which time her fluid intake was minimal. Eight hours prior to admission she noted malaise, tinnitus, and difficulty in hearing. At the time of admission, the temperature was 98° F.; pulse, 96; respirations, 20. A blood sample was obtained for study (Table I) prior to the start of therapy. The urine had a pH of 5.5 and gave a strongly positive ferric chloride test. Plasma CO_2 was 18.9 mM per liter; pH, 7.51; plasma salicylates, 51 mg. per cent. After treatment with oral fluids for twenty-four hours, a second blood sample was obtained for study (Table I). At that time plasma salicylates were 28 mg. per cent. Treatment with oral fluids resulted in complete recovery.

The mean plasma concentration of 17-hydroxycorticosteroids in normal children is nearly identical with that in normal adults, being 12.0 μg. per cent (SEM, 1.29; S.D., 8.2) in the former and 13.0 μg. per cent (SEM, 0.4; S.D., 6.0) in the latter.[18] Thus, each of the patients presented here had a markedly elevated circulating concentration of 17-hydroxycorticosteroids (Table II).

Fig. 1 shows 17-hydroxycorticosteroid concentrations found in the

plasma of guinea pigs at varying periods of time following the intraperitoneal injection of 75 mg. of sodium salicylate per animal. Guinea pigs were used because they, unlike rats and rabbits, have moderately high control levels of 17-hydroxycorticosteroids.[19] Significant elevations of these steroid levels were a consistent finding, with peak increases occurring at approximately four hours following the injection of salicylate.

In Table III are summarized the data concerning plasma 17-hydroxycorticosteroids in control guinea pigs

TABLE II. COMPARISON OF PLASMA 17-HYDROXYCORTICOSTEROID CONCENTRATIONS IN PATIENTS WITH SALICYLATE INTOXICATION AND IN NORMAL INDIVIDUALS

		NO. OF DETERMINATIONS	MEAN PLASMA 17-OH CORTICOSTEROIDS (μG./100 ML.)	S.E.M.	RANGE	P
Salicylate intoxication		7	38.9	±2.66	30.5-48.2	< .01
Normal individuals	Children	40	12.0	±1.29	0-28.7	
	Adults*	267	13	±0.4	2-34	

*Data from Reference 18.

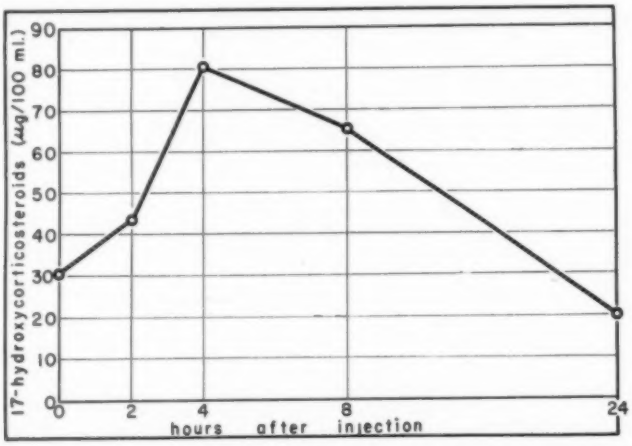

Fig. 1.—Plasma 17-hydroxycorticosteroids in guinea pigs following the intraperitoneal injection of 75 mg. sodium salicylate.

TABLE III. EFFECT OF SALICYLATE ADMINISTRATION ON PLASMA 17-HYDROXYCORTICOSTEROIDS IN GUINEA PIGS

TREATMENT*	NO. ANIMALS	MEAN PLASMA 17-OH CORTICOSTEROIDS (μG./100 ML.)	S.E.M.	P (VS. CONTROLS)
75 mg. Na salicylate in saline	15	81.8†	±12.05	< 0.01
25 mg. Na salicylate in saline	10	45.1†	± 6.99	0.16
$\frac{M}{6}$ Na lactate	12	30.6†	± 4.61	> 0.5
Controls (no treatment)	17	32.9	± 4.60	---

*Each solution was given intraperitoneally in a volume of 1 ml.
†Four hours after injection.

and in guinea pigs four hours after the intraperitoneal injection of sodium salicylate or sodium lactate. Neither those animals given M/6 sodium lactate, nor those given 25 mg. sodium salicylate in saline had 17-hydroxycorticosteroid concentrations significantly different from concentrations in the control group. However, the animals given 75 mg. sodium salicylate in saline exhibited highly significant elevations of these steroid levels (Table III).

DISCUSSION

Similarities between metabolic responses to salicylate administration and to the administration of ACTH or cortisone have been observed repeatedly.[1-14] However, the evidence that salicylates influence the pituitary-adrenal system, although suggestive, has been indirect and therefore inconclusive. The finding of significantly elevated plasma 17-hydroxycorticosteroid concentrations in patients with salicylate intoxication and in guinea pigs given large doses of salicylate offers the first direct evidence of the presence of increased concentrations of adrenal hormones in the circulation following salicylate administration. These observations tend to support the pituitary-adrenal stimulation concept of salicylate action; however, whether the increased concentrations of steroids noted are the result of a specific effect of salicylates on the pituitary-adrenal system, a nonspecific "stress" response, or an alteration in mechanisms concerned with removal of 17-hydroxycorticosteroids from the circulation cannot be determined from the data at hand.

Concentrations of 17-hydroxycorticosteroids comparable to or greater than those observed with salicylate intoxication are found consistently to follow ACTH administration.[20] Thus, it is possible that 17-hydroxycorticosteroid elevations of the magnitude observed in patients with salicylate intoxication may result from specific stimulation of the pituitary-adrenal system.

Conceivably, nonspecific "stress" might be the factor responsible for the high concentrations of 17-hydroxycorticosteroids observed here. However, patients with salicylate intoxication had circulating 17-hydroxycorticosteroid concentrations higher in general than those seen in patients clinically more severely ill during the acute phase of a variety of diseases.[15] The implication of "stress" alone would therefore necessitate the assumption that salicylate intoxication constitutes a "stress" more severe than is clinically apparent. Concentrations of 17-hydroxycorticosteroids higher than those seen in patients with salicylate intoxication have been reported to occur in "terminal" patients.[21] Whereas these elevations might be attributable solely to a more profound "stress," metabolic aberrations associated with the moribund state may interfere with the removal of 17-hydroxycorticosteroids from the circulation. The possibility that salicylate intoxication produces similar aberrations should be considered.

SUMMARY

Plasma 17-hydroxycorticosteroid concentrations were found to be elevated markedly in seven patients with salicylate intoxication and in guinea pigs given large doses of sodium salicylate intraperitoneally.

Guinea pigs given sodium lactate or smaller amounts of sodium salicylate, intraperitoneally, were found to have levels of these steroids which were not significantly different from those of untreated animals.

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REFERENCES

1. Roskam, J., and Van Cauwenberge, H.: Effect of Sodium Salicylate on Circulating Eosinophils and Urinary Uric Acid-Creatinine Ratio, Lancet **2**: 375, 1951.
2. Keleman, E., Majoros, M., Ivanyi, J., and Kovacs, K.: Salicylates, Stress and Cortisone, Experimentia **6**: 435, 1950.
3. Pasqualini, R. Q., Pasqualini, C., Dosne, de, and Garberi, J. C.: Action du Salicylate de Soude sur le Systeme Hypophysosurrenal, Compt. rend. Soc. biol. **145**: 122, 1951.
4. Pasqualini, R. Q., and Lascalea, M. C.: Tratemiento de la Fiebre Reumática con Salicilato de Sodio y Cloruro de Amonio, Prensa méd. argent. **35**: 1091, 1948.
5. Van Cauwenberge, H.: Relation of Salicylate Action to Pituitary Gland. Observations in Rats, Lancet **2**: 374, 1951.
6. Robinson, F. B.: Aspirin and the Adrenal Cortex, Brit. M. J. **1**: 300, 1951.
7. Cronheim, G., King, J. S., Jr., and Hyder, N.: Effects of Salicylic Acid and Similar Compounds on Adrenal-Pituitary System, Proc. Soc. Exper. Biol. & Med. **80**: 51, 1952.
8. Hetzel, B. S., and Hine, D. C.: The Effect of Salicylates on the Pituitary and Suprarenal Glands, Lancet **2**: 94, 1951.
9. Pasqualini, R. Q.: Corticotrofina y Salicilato de Sodio en el Tratemiento de la Fiebre Reumática, Rev. Asoc. méd. argent. **64**: 332, 1950.
10. Champy, C., and Demay, M.: Mode of Endocrine Action of Salicylates and Gentisates, J. A. M. A. **145**: 1365, 1951.
11. Van Cauwenberge, H., and Heusghem, C.: Acetylsalicylic Acid and the Urinary Excretion of Adrenocortical Steroids, Lancet **1**: 771, 1951.
12. Bertolani, F., Lorenzini, B., and Bonati, B.: Lancet (Letter to the Editor) **1**: 54, 1951.
13. Goodman, L.: The Pharmacological Basis of Therapeutics, New York, 1941, The Macmillan Co.
14. Reid, J., Watson, R. D., and Sproull, D. H.: The Mode of Action of Salicylate in Rheumatic Fever, Quart. J. Med. **19**: 1, 1950.
15. Ely, R. S., Kelley, V. C., and Raile, R. B.: Studies of 17-Hydroxycorticosteroids in Children. I. Peripheral Blood Levels in Health and Disease, J. PEDIAT. **42**: 38, 1953.
16. Nelson, D. H., and Samuels, L. T.: A Method for the Determination of 17-Hydroxycorticosteroids in Blood; 17-Hydroxycorticosterone in the Peripheral Circulation, J. Clin. Endocrinol. & Metab. **12**: 519, 1952.
17. Brodie, B. B., Undefriend, B., and Coburn, A. F.: Determination of Salicylic Acid in Plasma, J. Pharmacol. & Exper. Therap. **80**: 114, 1944.
18. Bliss, E. L., Sandberg, A. A., Nelson, D. H., Sweat, M. L., and Eik-Nes, K.: The Normal Levels of 17-Hydroxycorticosteroids in the Peripheral Blood of Man, J. Clin. Invest. **32**: 818, 1953.
19. Done, A. K., Ely, R. S., Raile, R. B., and Kelley, V. C.: Species Differences in Circulating 17-Hydroxycorticosteroid Concentrations, Proc. Soc. Exper. Biol. & Med. **81**: 667, 1952.
20. Raile, R. B., Ely, R. S., and Kelley, V. C.: Studies of 17-Hydroxycorticosteroids in Children. II. Response of Blood Levels to the Injection of Certain Hormones, J. PEDIAT. **42**: 46, 1953.
21. Nelson, D. H., Samuels, L. T., Willardson, D. G., and Tyler, F. H.: The Levels of 17-Hydroxycorticosteroids in Peripheral Blood of Human Subjects, J. Clin. Endocrinol. **11**: 1021, 1951.

INTESTINAL OBSTRUCTION IN INFANTS

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INTESTINAL obstruction in the newborn and infant age group is a commonly encountered problem in any hospital having an active pediatric service. The clinical picture of abdominal pain, vomiting, and frequently abdominal distention prompts the pediatrician to consult the radiologist who, as the middle man, is often faced with the difficult task of informing the waiting surgeon whether or not bowel obstruction is present. The responsibility lies with the radiologist. He is relied upon to make three major decisions, none of which is easy.

1. Is obstruction present?
2. What is the location of the obstructive lesion?
3. What is the etiology?

In regard to the first problem, one must be aware of the extreme normal variations of both the distribution and quantity of gas within the intestinal tract of infants and children in order to avoid pitfalls in diagnosis. According to Wasch and Marek,[1] gas reaches the proximal portion of the small bowel during the first hour of life and by three hours the entire small bowel contains gas. However, this time sequence is often delayed until the infant's first feeding, especially if the baby cries little during the interim. (Fig. 1.) But thereafter once the normal pattern is established, gas distributed within the small bowel is a normal finding throughout infancy. Typically the scout films of the normal newborn and young infant show the small bowel gas pattern as multiple ill-defined areas of radiolucency confined for the most part to the left side of the abdomen. The bowel is not distended and definite continuity of loops is undetectable. Such a picture is unequivocally normal. Occasionally, however, an excessive amount of gas may be seen in the small intestine of an infant who, for some reason, has swallowed a great deal of air. The intestinal loops may even be distended. In such cases gas is also present within the stomach and colon, presenting an appearance which may simulate exactly an early low mechanical obstruction, or paralytic ileus. Follow-up films may be necessary to determine if the distention is progressing before an obstructive lesion can be definitely ruled out. (Fig. 2.)

After the child begins walking and spending less time in the recumbent position, the gas collects for the most part in the stomach and colon, i.e., attains an adult type of distribution. However, the presence of gas, even in moderate amounts in the small bowel of a young child past the infant stage, should not in itself cause alarm. The amount of crying and the number of hours spent in the recumbent position may all affect the amount of gas within the small bowel of this older age group. Clinical evidence of obstruction must be present for such a

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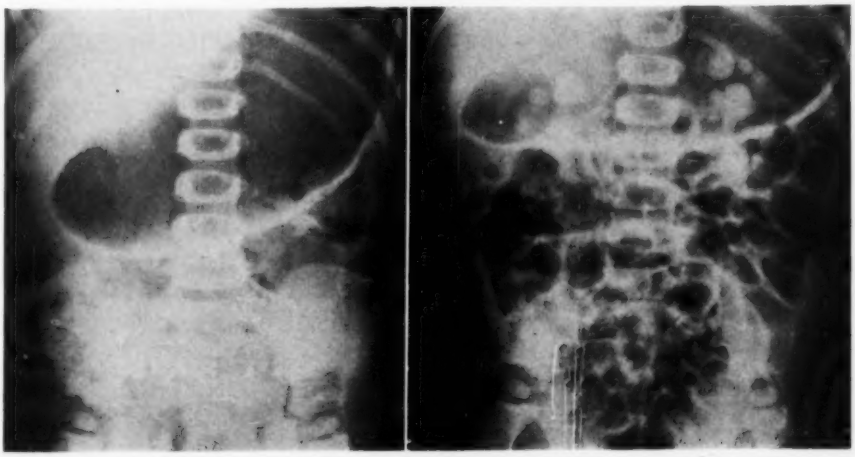
Fig. 1.—Sequence of films made on newborn infant from time of birth to 17 hours after birth. Gas did not accumulate in the alimentary tract in significant amounts until after the first feeding at 11 hours. The infant cried little and slept during the first hours of life, thereby producing the delay in the appearance of the swallowed air.

finding to be significant (Figs. 3 and 4).

Fluid levels within both colon and small bowel are not infrequently seen in nonobstructed infants when films are taken with the patient in an upright position. This is especially noticeable in an infant with diarrhea which if not obvious clinically will be forthcoming within a few hours after the examination. Such cases may also show a considerable amount of intestinal gas manifested clinically by actual abdominal distention (Fig. 5).

A. *B.*

Fig. 2.—*A*, The scout film of a 6-month-old baby made following a convulsion. The appearance is that of paralytic ileus or low mechanical obstruction. Clinically, abdominal distention was present but there were no other signs or symptoms of intestinal obstruction. *B*, Follow-up film made a day later shows no abnormality. Presumably the infant swallowed an excessive amount of air during the convulsion.



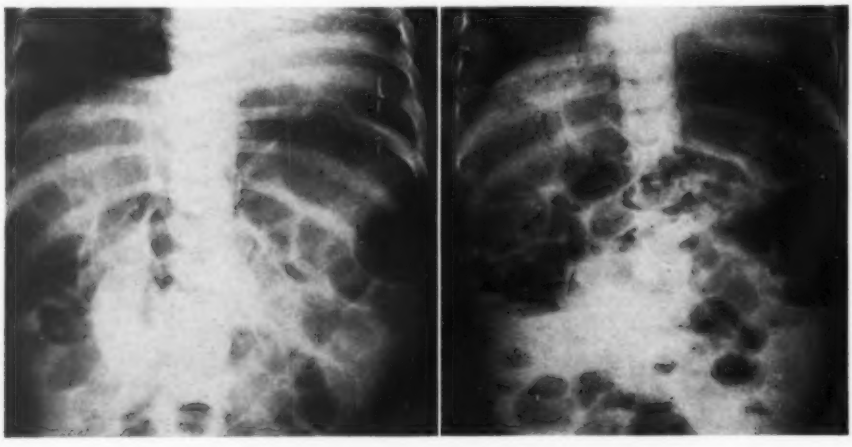
A. *B.*

Fig. 3.—*A*, Example of rapid accumulation of air within stomach and *B*, five minutes later within small bowel of a 3-year-old child who was crying violently during an excretory pyelogram examination.

Each of us is familiar with the cardinal radiographic signs of intestinal obstruction—the distention of bowel, continuity of loops, "hairpin turns," the stepladder formation of parallel segments of bowel and air-fluid levels. But, as we have seen, several of these signs may be found in the scout films of infants and children who do not have intestinal obstruction. Therefore, before a diagnosis is offered, there must be accurate correlation of these signs with the clinical picture. Unless this is done, the radiologist may be led astray by the variable and often equivocal scout film.

Fig. 4.—Example of accumulation of gas in small bowel in an individual who remains in the recumbent position. The patient was an 8-year-old boy who was ill with endocarditis.

Having established this diagnosis, the radiologist is faced with the other two problems—the location and etiology of the obstruction. Both of these questions are more difficult to answer than establishing the presence of obstruction. Nevertheless an attempt should be made to determine if the obstruction is in the colon, low small bowel, high small bowel, or at the gastric outlet. Once this is established a more reasonable differential diagnosis can be considered in regard to



A. *B.*

Fig. 5.—*A*, Recumbent scout film of a 16-month-old baby who clinically had abdominal distention and diarrhea. *B*, Upright film shows numerous air-fluid levels.

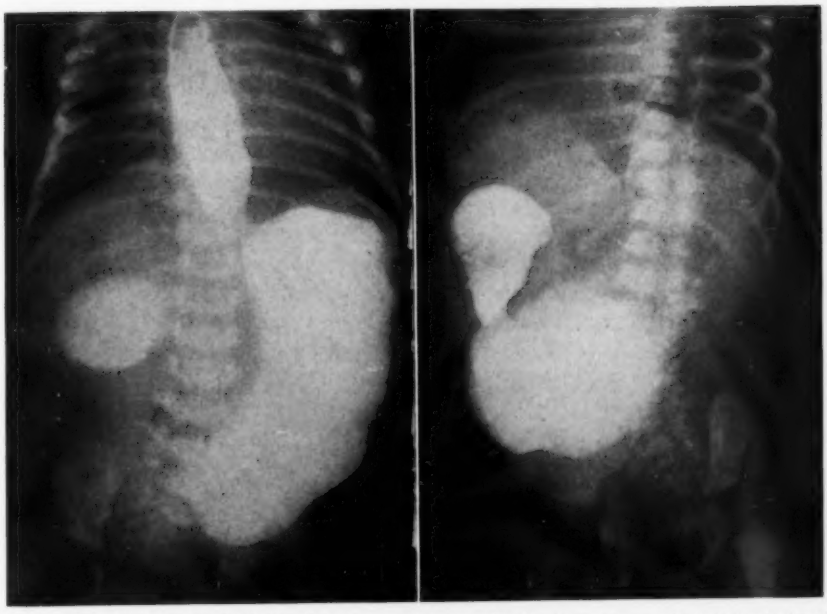


Fig. 6.—Complete duodenal obstruction in a newborn infant. Laparotomy disclosed duodenal atresia.

the etiology. It is beyond the scope of this report to cover the many causes of intestinal obstruction occurring in infants. Therefore only the congenital lesions will be considered.

Obstruction in the duodenum usually offers no problem. The confusing fortuitous gas patterns of distended gut encountered in lower obstructive lesions are not present and it is the conspicuous absence or decrease of gas in the abdomen which leads to the diagnosis. Frequently the stomach and that part of the duodenum proximal to the obstruction are distended. Clinically, vomiting is severe but distention is not a conspicuous feature. If the vomitus is bile stained, one may assume that the obstruction is below the ampulla of Vater. Examination with contrast material is usually unnecessary, the gas in the distended bowel providing accurate localization

Fig. 7.—Duodenal obstruction due to congenital peritoneal band. Note that contrast material succeeded in passing the site of obstruction whereas air was held back.

of the lesion. This combination of roentgenographic and clinical findings in a newborn infant is indicative of a congenital obstructive lesion of the duodenum. The lesion may be atresia, stenosis, peritoneal band, or volvulus. If a small amount of gas is seen scattered throughout the bowel distal to the distended segment, atresia is eliminated from the differential diagnosis. The absence of this sign, however, does not exclude stenosis or a peritoneal band as evidenced by the occasional lesion which although prohibiting the passage of air, allows contrast material once ingested to pass the site of obstruction. Presumably this is the result of the heavier bolus being more actively propelled through the gut (Figs. 6 and 7). Congenital volvulus due to faulty rotation of the midgut with torsion about the axis of the superior mesenteric artery produces obstruction in the duodenum usually in its third portion. Roentgenograms of the abdomen are similar to the cases of duodenal atresia. A helpful sign in the diagnosis of obstruction secondary to volvulus or peritoneal band is the demonstration of either malposition or abnormal mobility of the cecum by barium enema studies. Such a finding denotes incomplete fixation of the base of the mesentery secondary to malrotation of the midgut. According to Silverman and Caffey,[3] the peritoneal bands which are found commonly accompanying this condition and which may be the direct cause of obstruction represent distorted at-

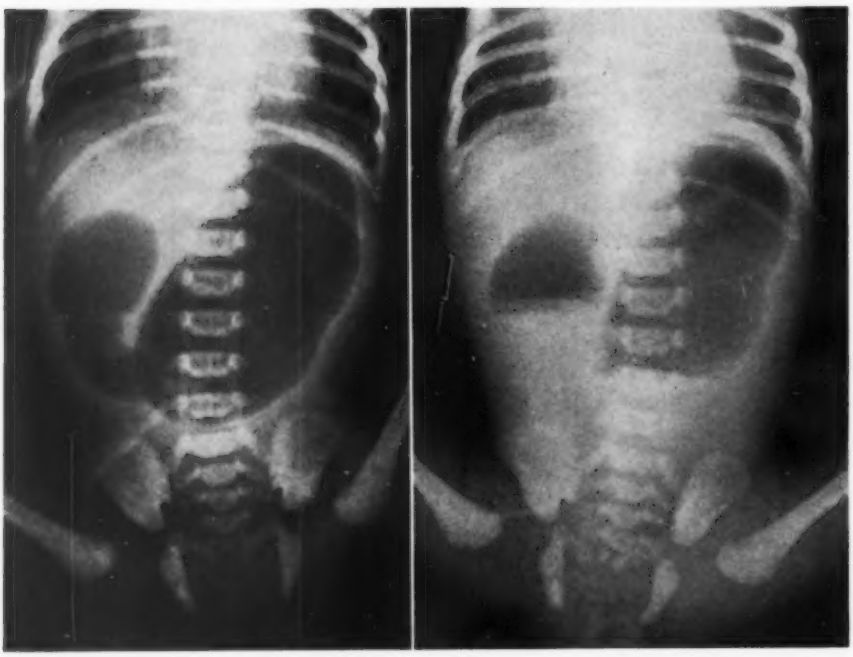


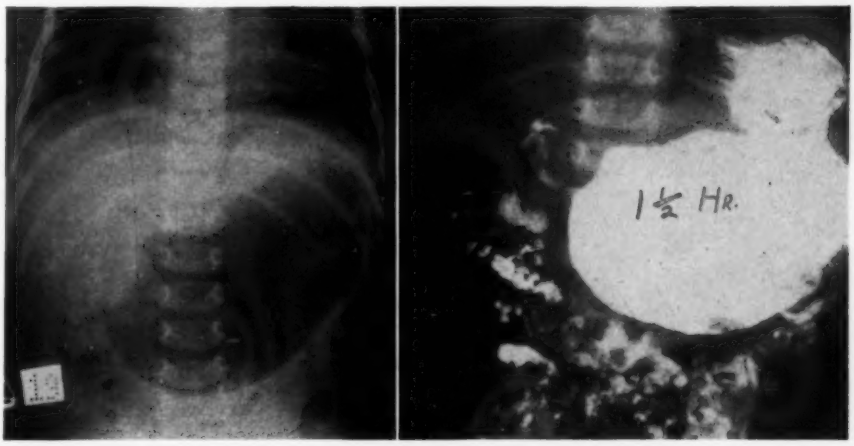
Fig. 8.—Congenital obstruction of the duodenum by annular pancreas.

tempts of fusion or failure of absorption of the malpositioned peritoneal structures. However, it hardly seems justifiable to subject the infant to a colon examination thereby postponing laparotomy in an effort to determine more accurately the cause of the duodenal obstruction.

Annular pancreas is a rare cause of congenital duodenal obstruction and produces the same radiographic findings as congenital stenosis or atresia depending on the severity of the lesion (Fig. 8).

of a small amount of contrast material, are diagnostic features (Fig. 9).

The lower the obstructive lesion in the small bowel, the more difficult it is to localize accurately the site of obstruction. The clinical picture may be more helpful, distention being more prominent and vomiting less frequent the lower the lesion. As the intestinal loops become distended with air, they are displaced from their normal position so that the problem of identifying segments of bowel on the basis of their position in the abdomen



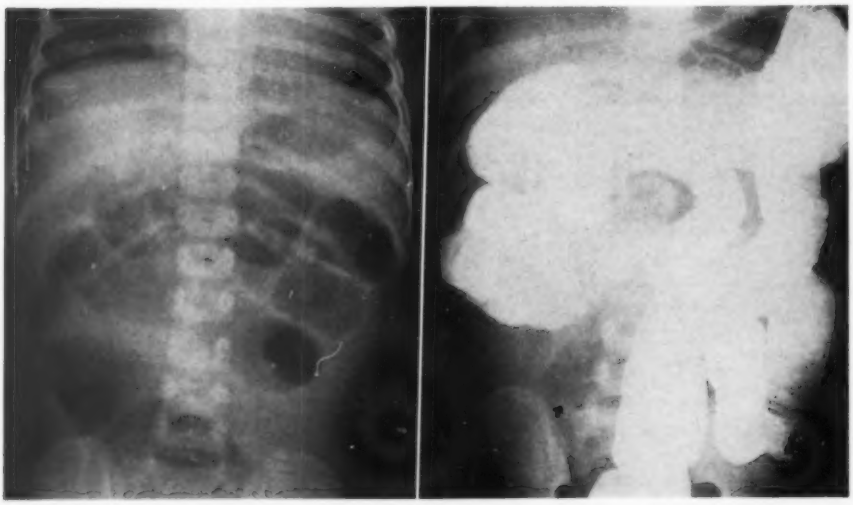
A. *B.*

Fig. 9.—Hypertrophic pyloric stenosis. The elongated pyloric canal can be identified on the preliminary scout film (*B*). Contrast material in the stomach shows the elongated pyloric canal and delayed emptying.

Hypertrophy of the pyloric muscle with resulting obstruction is generally considered to be a congenital lesion and is therefore included in this discussion. Symptoms usually occur a few weeks after birth, and the over-all clinical picture is characteristically diagnostic. Radiographic studies and fluoroscopy are confirmatory. The stomach is dilated and the narrow elongated pyloric canal, demonstrated after the ingestion

becomes impossible. However, in cases of obstruction involving the jejunum, an upright film may be helpful by showing the gas-filled loops confined to the upper portion of the abdominal cavity. As the obstructive lesion persists, fluid collects in many of the loops, obliterating them as identifiable segments of bowel and giving the impression that the lesion is at a higher level than is actually the case. In

early obstruction the pattern of the bowel may be helpful in locating the site of the obstruction, the prominent deep plicae of the jejunal mucosa being differentiated from the smoother mucosa of the ileum. Unfortunately, however, distention of the gut flattens out these folds, producing a smooth outline in all segments of the small bowel. If the colon can be identified by its peripheral location and haustral markings, one can be reasonably certain that the obstruction is not in the small bowel. If the colon cannot be identified with certainty, barium enema studies should be carried out. If the colon is normal, the obstruction is in the small bowel. A small amount of contrast substance may be given by mouth to determine the exact site of obstruction. This, however, only serves to satisfy the academic mind and results in unnecessary delay of the surgical intervention. Obstructive lesions of the ileum, if seen in the early stages, show the abdomen to be filled with gas-distended loops of intestine. Consequently it is often impossible to accurately outline the colon, and what may appear to be colon is actually distended ileum. This mimicry is especially noticeable in the lateral view where the distended ileum is seen to lie parallel to the anterior abdominal wall. Again, barium enema will serve to locate the colon, thereby identifying the lesion as being in the distal small bowel.



A. *B.*

Fig. 10.—*A*, Scout film of a 1½-year-old boy who had symptoms of intestinal obstruction. Note the distended air pouch in the lower abdomen. *B*, Displacement of the cecum by the duplicated segment of ileum.

Etiological possibilities to be considered in mid and low small bowel obstruction are as numerous as those causes already mentioned. Atresia and stenosis should always be considered. Herniation of the small intestine through mesenteric defects with resulting strangulation of the gut is an

uncommon cause of obstruction and usually diagnosed only at the time of surgery. A duplicated segment of ileum may, if it becomes distended with secretions, obstruct the adjacent normal segment.[4] The duplicated segment may also produce a volvulus. This should be suspected in an obstructed patient whose scout film shows persistence of a distended loop of gut in the lower abdomen following decompression of the other dilated segments by means of intestinal intubation. Fig. 10 shows the scout film and barium enema studies on a 1½-year-old boy who had symptoms of intestinal obstruction. A gas-containing pouch in the lower abdomen is clearly defined on all of the films and displaces the cecum upward. Fig. 11 shows the resected specimen. The distended pouch was lined with gastric mucosa and a peptic ulcer was found in the normal ileum opposite the opening which led into the lumen of the duplicated segment.

Congenital functional intestinal obstruction as described by Zuelzer and Wilson[5] may be another cause of low small bowel obstruction. In such cases there is neuromuscular dysfunction of a portion of the bowel incident to congenital absence of ganglion cells in the myenteric plexus. The abnormality may also affect any level of the colon.

Fig. 11.—Resected specimen of the case shown in Fig. 10. Through the opening into the duplicated segment of ileum, gastric mucosal folds can be seen. An area of peptic ulceration is seen opposite this opening in the normal ileum (upper probe).

Infants with this disorder usually have a history of chronic constipation and abdominal distention dating from birth, but more severe cases have symptoms indistinguishable from acute mechanical obstruction. The scout films of such infants show distended loops of bowel, the distention being proximal to the aganglionic segment. Organic obstruction cannot be demonstrated but if the abnormal segment

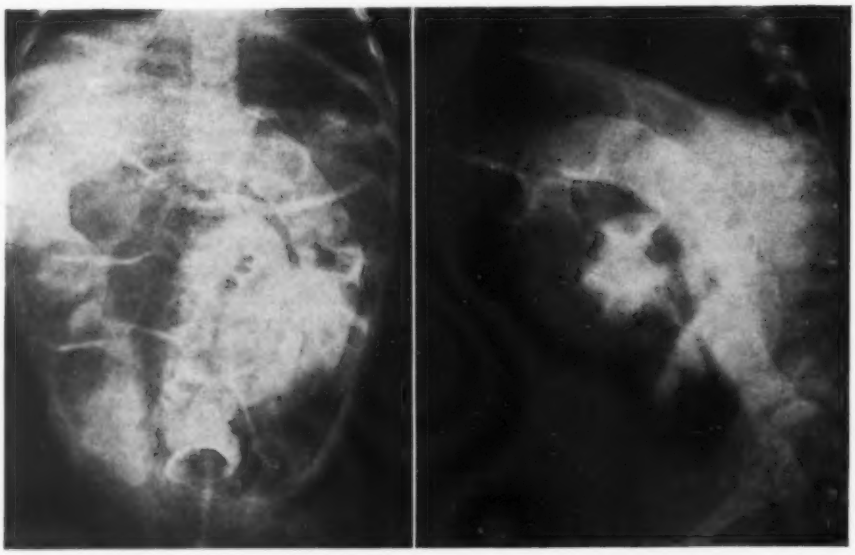


Fig. 12.—Congenital functional intestinal obstruction due to congenital absence of ganglia cells in the terminal ileum. The colon as outlined with barium is normal. Note the distended ileum paralleling the anterior abdominal wall in the lateral view.

Fig. 13.—Meconium ileus. The small size of the colon is the result of intestinal contents never having passed through it.

is located in the colon or terminal ileum, the change from narrow to distended bowel can be demonstrated by barium enema. Fig. 12 is one of the cases originally reported by Zuelzer and Wilson. The patient was a 5-month-old female infant who had showed progressive abdominal distention and constipation since birth. Barium enema studies showed no abnormality of the colon. The large number of dilated intestinal loops denotes obstruction in the distal portion of the small bowel. The dilated bowel seen in lateral view paralleling the anterior abdominal wall and frequently mistaken for colon is ileum.

Meconium ileus should be considered in all newborn cases having clinical and radiographic signs of low intestinal obstruction. In such cases the meconium is thick and viscid as the result of underlying mucoviscidosis or

pancreatic disease. Peristalsis is unable to push this tenacious material through the intestine and obstruction results, usually in the terminal ileum. Roentgenograms show distended loops of bowel similar to other causes of ileal obstruction. Occasionally a mottled pattern can be identified which Neuhauser[6] has described as being a mixture of air and meconium. The colon in such cases, when outlined with barium, appears unusually small (Fig. 13). Associated atresia of the ileum has been reported frequently in this condition and may actually represent cicatricial changes in the bowel resulting from trauma produced by peristaltic action on the hard tenacious meconium rather than primary atresia.[7] Peritoneal calcification secondary to in utero meconium peritonitis is a frequent associated finding. Recently it has been shown that calcification of meconium may occur within the bowel lumen.[8]

Anomalies of the colon which produce complete obstruction lead to marked abdominal distention. Scout films show the abdominal cavity to be filled with gas-distended loops of bowel and many fluid levels will be seen in upright films. Barium enema studies will determine the exact location of the obstructing lesion. Although areas of atresia or stenosis may produce obstruction, more common causes are Hirschsprung's disease and imperforate anus. The former condition is difficult to diagnose in the newborn period for the time interval has not

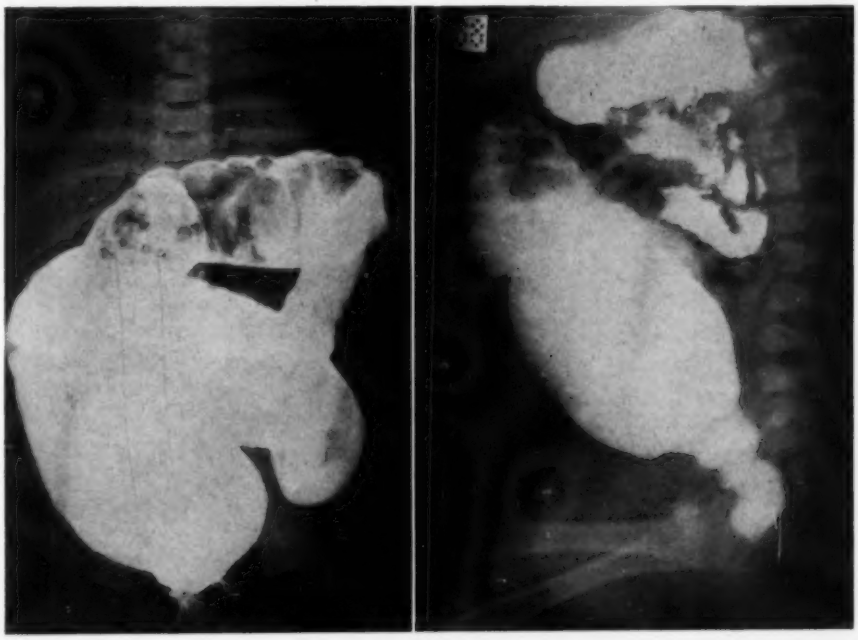
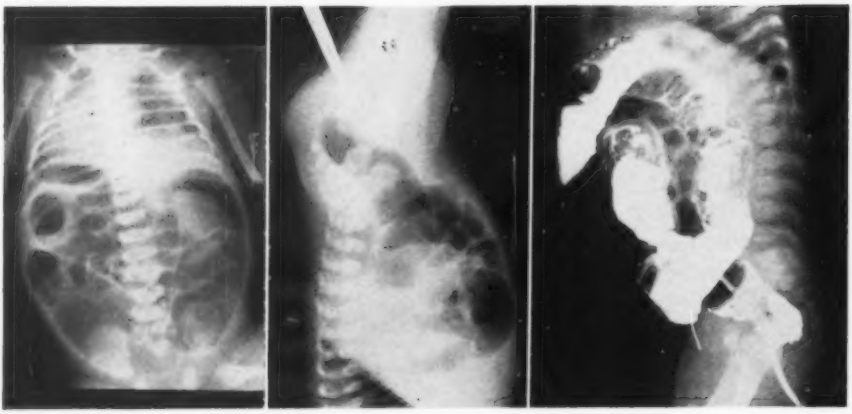


Fig. 14.—Hirschsprung's disease in a 3-month-old child. The value of the lateral view is apparent in demonstrating the transitional zone from rectum to dilated sigmoid.



A. *B.* *C.*

Fig. 15.—Imperforate anus. *A*, Scout film shows marked distention of colon as well as considerable gas in small bowel. *B*, Film made with patient in inverted position shows distance between gas in rectum and probe at anal orifice. *C*, Film made postoperatively showing reconstruction of passageway.

Fig. 16.—Congenital rectoanal stricture in a 1-month-old child. Repeated dilatations were carried out for several years. Finally plastic repair was performed.

been sufficient to allow for dilatation of the colon, a finding which is quite characteristic in later life. If the condition is suspected, a barium enema may show the narrow aganglionic rectosigmoid segment early in life. Fig. 14 shows a barium enema examination on a 3-month-old child. The value of the lateral view is clearly demonstrated by showing the abrupt transition from rectum to dilated sigmoid, a finding not appreciated in the frontal view.

Imperforate anus is usually diagnosed clinically. Scout films may show considerable dilatation of the colon. Films made with the infant in an inverted position characteristically show the distance between gas in the rectum and the anus. However, if meconium lies in the rectum just above the site of imperforation, the actual distance may be less than is apparent. Rectovesical or rectourethral fistula is a common associated finding in males with this anomaly, and, in such cases, roentgenograms will show air in the urinary bladder. (Fig. 15.)

Congenital stricture of the rectum is a rare cause of partial obstruction and clearly demonstrated after the injection of contrast material into the rectum (Fig. 16).

In conclusion, the radiologist who is called upon for consultation regarding intestinal obstruction in the newborn and infant age groups must carefully consider the clinical history before making a diagnosis of intestinal obstruction. Once the diagnosis of obstruction is established, the location of the lesion should be determined on the basis of the location and distribution of gas in the intestine, the mucosal pattern of the distended loops, and, if necessary, by studies using contrast material. A complete knowledge of etiological possibilities is necessary to complete the radiologists' responsibilities in the evaluation of such cases.

REFERENCES

1. Wasch, M. G., and Marck, A.: The Radiographic Appearance of the Gastrointestinal Tract During the First Day of Life, J. PEDIAT. **32**: 479, 1948.
2. Storch, C., Redner, B., and Turin, R. D.: Small Bowel Obstruction in Infancy and Childhood, J. PEDIAT. **35**: 366, 1949.
3. Silverman, F. N., and Caffey, John: Congenital Obstructions of the Alimentary Tract in Infants and Children: Errors of Rotation of the Midgut, Radiology **53**: 781, 1949.
4. Gross, R. E., Holcomb, G. W., Jr., and Farber, S.: Duplication of the Alimentary Tract, Pediatrics **9**: 449, 1952.
5. Zuelzer, W. W., and Wilson, J. L.: Functional Intestinal Obstruction on a Congenital Neurogenic Basis in Infancy, Am. J. Dis. Child. **75**: 40, 1948.
6. Neuhauser, E. B. D.: Roentgen Changes Associated With Pancreatic Insufficiency in Early Life, Radiology **46**: 319, 1946.
7. Kasmersky, C. T., and Howard, W. H. R.: The Significance of Intra-abdominal Calcification in the Newborn Infant, Am. J. Roentgenol. **68**: 395, 1952.
8. Bruwer, Andre, and Hodgson, J. R.: Intestinal Obstruction in Fibrocystic Disease of the Pancreas, Am. J. Roentgenol. **69**: 14, 1953.

INTRAMUSCULAR TERRAMYCIN: LABORATORY AND CLINICAL STUDIES IN CHILDREN

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THREE and one-half years following the introduction of Terramycin for general clinical use, and after a carefully planned research program,[1, 2, 3, 4, 5, 6] it has been firmly established as a potent therapeutic agent in the treatment of acute and chronic infections, caused by bacterial, rickettsial, spirochetal, protozoan, and some viral organisms.

The minimal inhibitory concentration of Terramycin for the majority of the susceptible organisms, ranges from 0.3 μg to 5.5 μg per cubic centimeter.[2] Serum and cerebrospinal fluid levels were determined in children by Hunt and associates[7] after the administration of single oral doses of 11, 22, 33, and 66 mg. per kilogram of body weight. Single oral doses of 11 mg. per kilogram gave peak levels ranging from 0.2 to 1.95 μg per cubic centimeter with a mean of 1.0 μg cubic centimeter and declined six hours after the ingestion. Single doses of 22 and 33 mg. resulted in insignificant changes. A dose of 66 mg. per kilogram caused significant elevation of serum levels. The cerebrospinal fluid levels determined in three normal patients, five hours after an oral dose of 33 mg. per kilogram, ranged from less than 0.4 to 0.56 μg per cubic centimeter, which was less than one-fourth to one-eighth of serum levels. When Terramycin was given intravenously to children in dosage of 6.6 mg. per kilogram, mean serum levels of 10.6 μg at one-half hour, 2.9 μg at six hours, and 1.17 μg per cubic centimeter at twelve hours were obtained.

The aim of this study, which was done in the pediatric age group, is to present data on serum and cerebrospinal fluid levels after the intramuscular administration of Terramycin, to describe the influence of dosage upon local tolerance, and present the results of a clinical trial in forty-five patients.

MATERIAL AND METHODS

The concentrations of Terramycin in serum and cerebrospinal fluid were determined in the laboratories of Chas. Pfizer & Co., Inc., by the turbidimetric bioassay method which has been described by Kersey.[8] The drug was supplied in vials containing Terramycin Hydrochloride 250 mg., magnesium chloride hexahydrate 250 mg., and procaine hydrochloride. It was administered to convalescent or normal children, who were free of renal or cardiac disease. The injections were given between 9:00 A.M. and 11:00 A.M., deep into the gluteal muscles, with a 20 to 22 gauge, 1¼ inch needle, and the concentration of Terramycin used was 100 mg. per cubic centimeter. The number of bioassays performed was 240. The ages of the sixty-three children used in this study ranged between 6 days and 13 years.

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SERUM AND CEREBROSPINAL FLUID TERRAMYCIN LEVELS

In fifty children who were on various dosage schedules, serum levels were determined, one, eight, twelve and twenty-four hours after injections. As shown in Table I a single dose of 3 mg. per kilogram was injected into ten children whose ages ranged between 3 months and 13 years. The peak levels, one hour after injection, ranged between 0.6 and 2.5 μg per cubic centimeter. A concentration of 0.3 μg per cubic centimeter or higher was present in nine cases twelve hours after injection. In only three cases was a detectable concentration (0.1 μg per cubic centimeter) obtained after twenty-four hours. In ten patients given the dosage of 6 mg. per kilogram the mean eight- and twelve-hour levels were almost the same (Table II). The peak level ranged between 1.2 and 2.5 μg per cubic centimeter and started to decline one hour after injection. In eight cases a twenty-four-hour level of 0.3 μg was obtained. The mean one-, eight-, twelve-, and twenty-four-hour levels were twice as high as those obtained with a 3 mg. dose. By increasing the dose to 12.5 mg. (Table III), the average serum levels at one, eight, and twelve hours were doubled. The peak levels were noticed one hour after injection and ranged between 1.2 and 5 μg. A dose of 25 mg. was injected into ten children (Table IV), resulting in peak levels at one hour, ranging between 5 and 10 μg. The mean one-hour level was almost three times as high as after the injection of the 12.5 mg.

TABLE I. SERUM TERRAMYCIN LEVELS, SINGLE DOSE 3 MG. PER KILOGRAM

PATIENT	WEIGHT (KG.)	AGE	DOSE (MG.)	SERUM LEVEL μG/C.C. HOUR AFTER INJECTION			
				1	8	12	24
1	6	3 mo.	18	1.2	1.2	0.6	0
2	14	3 yr.	42	0.6	0.3	0.3	0
3	23	7 yr.	69	1.2	0.3	0.3	0
4	24	6 yr.	72	0.6	0.6	0.3	0
5	25	10 yr.	75	0.6	0.3	0.6	0.3
6	27	8 yr.	81	0.6	0.3	0.3	0
7	28	10 yr.	84	0.6	0.3	0.3	0.1
8	28	11 yr.	84	0.6	0.3	0.3	0.1
9	37	12 yr.	110	0.6	0.3	0	0
10	40	13 yr.	120	2.5	0.6	1.2	0.1
Mean serum level				0.91	0.45	0.42	0.06

TABLE II. SERUM TERRAMYCIN LEVELS, SINGLE DOSE 6 MG. PER KILOGRAM

PATIENT	WEIGHT (KG.)	AGE	DOSE (MG.)	SERUM LEVEL μG/C.C. HOUR AFTER INJECTION			
				1	8	12	24
1	3	6 da.	18	2.5	1.2	0.6	0.6
2	8	9 mo.	48	2.5	1.2	0.3	0.3
3	13	3 yr.	78	1.2	0.6	0.6	0.1
4	16	3 yr.	96	1.2	0.6	0.6	0.3
5	19	4 yr.	104	2.5	1.2	1.2	0.3
6	20	7 yr.	120	2.5	1.2	0.6	0.0
7	27	8 yr.	162	2.5	1.2	0.6	0.3
8	33	11 yr.	200	1.2	0.6	0.6	0.3
9	35	11 yr.	210	1.2	1.2	0.6	0.3
10	35	11 yr.	210	2.5	1.2	1.2	0.3
Mean serum level				1.98	1.02	0.69	0.30

TABLE III. SERUM TERRAMYCIN LEVELS, SINGLE DOSE 12.5 MG. PER KILOGRAM

PATIENT	WEIGHT (KG.)	AGE	DOSE (MG.)	SERUM LEVEL μG/C.C. HOUR AFTER INJECTION			
				1	8	12	24
1	3	3 wk.	37.5	5.0	2.5	1.2	0.6
2	10	9 mo.	125	5.0	1.2	0.6	0.3
3	18	5 yr.	225	2.5	1.2	1.2	0.3
4	19	7 yr.	238	5.0	1.2	0.6	0.6
5	20	6 yr.	250	1.2	0.6	0.3	0.1
6	21	6 yr.	262	2.5	2.5	1.2	0.6
7	23	10 yr.	290	5.0	2.5	2.5	1.2
8	24	8 yr.	300	2.5	1.2	1.2	0.6
9	24	9 yr.	300	2.5	1.2	2.5	0.1
10	26	11 yr.	325	5.0	2.5	1.2	0.6
Mean serum level				3.62	1.66	1.25	0.40

TABLE IV. SERUM TERRAMYCIN LEVELS, SINGLE DOSE 25 MG. PER KILOGRAM

PATIENT	WEIGHT (KG.)	AGE	DOSE (MG.)	SERUM LEVEL μG/C.C. HOUR AFTER INJECTION			
				1	8	12	24
1	9	18 mo.	225	10.0	2.5	2.5	1.2
2	10	2 yr.	250	10.0	1.2	0.6	0.6
3	10	4 yr.	250	5.0	2.5	1.2	0.6
4	11	2 yr.	275	10.0	2.5	1.2	0.6
5	15	5 yr.	375	10.0	5.0	2.5	1.2
6	17	6 yr.	425	10.0	5.0	2.5	1.2
7	18	6 yr.	450	10.0	5.0	2.5	1.2
8	20	6 yr.	500	10.0	5.0	2.5	1.2
9	24	9 yr.	600	10.0	2.5	2.5	1.2
10	35	8 yr.	875	10.0	5.0	2.5	1.2
Mean serum level				9.50	3.62	2.05	1.02

TABLE V. SERUM TERRAMYCIN LEVELS, SINGLE DOSE 50 MG. PER KILOGRAM

PATIENT	WEIGHT (KG.)	AGE	DOSE (MG.)	SERUM LEVEL μG/C.C. HOUR AFTER INJECTION			
				1	8	12	24
1	8	6 mo.	400	40.0	20.0	10.0	2.5
2	11	15 mo.	550	40.0	20.0	20.0	10.0
3	13	21 mo.	650	20.0	10.0	2.5	2.5
4	13	2 yr.	650	20.0	10.0	5.0	2.5
5	14	2 yr.	750	20.0	10.0	10.0	5.0
6	14	3 yr.	700	10.0	40.0	20.0	2.5
7	16	2½ yr.	800	20.0	10.0	5.0	2.5
8	16	6 yr.	800	20.0	10.0	2.5	2.5
9	17	7 yr.	850	20.0	5.0	5.0	2.5
10	22	7 yr.	1100	5.0	10.0	5.0	2.5
Mean serum level				21.5	14.5	8.5	3.50

TABLE VI. SERUM TERRAMYCIN LEVELS, 15 AND 30 MINUTES AFTER INJECTION

PATIENT	DOSE (MG./KG.)	TOTAL DOSE (MG.)	WEIGHT (MG.)	AGE	SERUM LEVEL μG/C.C. MINUTES AFTER INJECTION	
					15	30
1	3	66	22	8 yr.	0.6	0.6
2	6	102	18	5 yr.	1.2	1.2
3	12.5	237	19	5 yr.	5.0	2.5
4	25.0	200	8	1½ yr.	10.0	10.0
5	50.0	500	10	2 yr.	40.0	40.0
6	50.0	700	14	3 yr.	<80.0	40.0

TABLE VII. SERUM AND CEREBROSPINAL FLUID TERRAMYCIN LEVELS

PATIENT	WEIGHT (KG.)	AGE	TOTAL DOSE (MG.)	SERUM LEVEL μG/C.C. HOUR AFTER INJECTION		CSF LEVEL μG/C.C. HOUR AFTER INJECTION	
				1 HR	8 HR.	1 HR	8 HR.
1*	9	18 mo.	225	10.0	2.5	1.25	0.31
2*	17	6½ yr.	850	10.0	5.0	0	0.15
3†	13	21 mo.	650	20.0	10.0	0	0.15

*Single dose, 25 mg. per kilogram.
†Single dose, 50 mg. per kilogram.

per kilogram dose. The mean twenty-four-hour level was 1.02 μg per cubic centimeter which was twice as high as with the 12.5 mg. dose.

Ten children who received a dose of 50 mg. per kilogram had peak

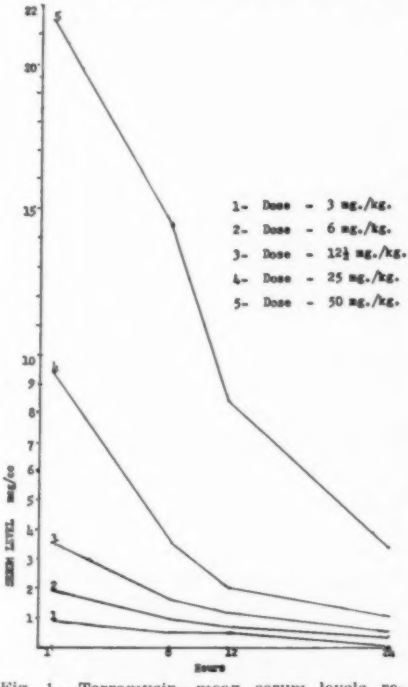

Fig. 1.—Terramycin—mean serum levels, resulting from different dosages.

levels ranging between 5 and 40 μg per cubic centimeter one hour after administration of the drug. In two cases the eight-hour level was higher than the one-hour level. The mean twenty-four-hour level was 3.5 μg per cubic centimeter.

Determinations were done with the same dosage in four other children, thirty-six and forty-eight hours after administration of the drug. The concentration was 0.31 μg per cubic centimeter at thirty-six hours in two cases. No traces of Terramycin were detectable at the end of forty-eight hours. A graphic illustration of mean serum levels with various dosages is shown in Fig. 1. The absorption of Terramycin into the blood stream was very rapid, as shown in Table VI. The fifteen- and thirty-minute levels obtained after administration of 3, 6, 12.5, 25, and 50 mg. per kilogram doses were as high as, or even higher than, those obtained at one hour.

In three normal children the diffusibility into the cerebrospinal fluid was poor (Table VII). Case 1 received a dose of 25 mg. per kilogram and his cerebrospinal fluid level at one and eight hours was higher than the other two children who received a dose of 50 mg. per kilogram.

LOCAL TOLERANCE

In order to determine the influence of Terramycin upon local tolerance, daily examination of the buttocks was performed. The degree of pain, tenderness, redness, swelling or induration, if present, were described. The local reaction was classified as *severe* (redness, swelling, severe pain, and tenderness), *moderate* (slight swelling, moderate pain, and tenderness), and *mild* (mild tenderness). Injections

were given to eighty-one patients of which seventeen had local reactions. Three of them had severe reactions, four moderate, and ten mild. In the first group of thirty-six patients receiving a single injection, only six complained of pain or tenderness, or had slight swelling, which persisted for one day. The single dose in these six cases ranged between 700 and 1,100 mg. In cubic centimeter into the right buttock, with the total dose being the same. In using these two concentrations, no significant difference in local reaction was noted. However, there were other factors which determined the frequency of local reactions; namely, the interval between injections, the number of injections, the total dose, and the patient's age. As

TABLE VIII. THE RELATION OF LOCAL REACTION TO INTERVAL BETWEEN INJECTIONS IN FORTY-FIVE PATIENTS

INTERVAL BETWEEN INJECTIONS	NUMBER OF PATIENTS	PER CENT OF PATIENTS WITH LOCAL REACTION	DEGREE OF LOCAL REACTION IN NUMBER OF PATIENTS		
			SEVERE	MODERATE	MILD
12 hr.	18	44	2	3	3
24 hr.	27	11	1	–	2

TABLE IX. THE RELATION OF LOCAL REACTION TO NUMBER OF INJECTIONS GIVEN IN EIGHTY-ONE PATIENTS

NUMBER OF INJECTIONS	NUMBER OF PATIENTS	PER CENT OF PATIENTS WITH LOCAL REACTION	DEGREE OF LOCAL REACTION IN NUMBER OF PATIENTS		
			SEVERE	MODERATE	MILD
0-3	51	11	–	1	5
3-10	23	30	2	1	4
Over 10	7	57	1	2	1

TABLE X. THE RELATION OF LOCAL REACTION TO TOTAL TERRAMYCIN (DOSE IN MG.) IN EIGHTY-ONE PATIENTS

TOTAL DOSE (MG.)	NUMBER OF PATIENTS	PER CENT OF PATIENTS WITH LOCAL REACTION	DEGREE OF LOCAL REACTION IN NUMBER OF PATIENTS		
			SEVERE	MODERATE	MILD
1-500	43	4	–	–	2
500-1,000	24	25	–	2	4
Over 1,000	14	64	3	3	3

the second group of forty-five patients, who received multiple injections given at twelve- or twenty-four-hour intervals, eleven showed signs of local irritation. Of this group, three patients had severe reactions, three moderate, and five mild. An attempt was made to evaluate the influence of concentration of the drug on local tolerance. Each patient received the drug in concentration of 75 mg. per cubic centimeter into the left buttock, alternating with the concentration of 100 mg. per

shown in Table VIII, a group of eighteen patients who received the injections at twelve-hour intervals, 44 per cent had signs of local irritation. In a group of twenty-seven patients who were injected at twenty-four-hour intervals with approximately the same total dose, only 11 per cent showed local reaction. Tables IX and X illustrate the relation of local reaction to the number of injections and the total dose. Two-thirds of the patients who received more than ten injections or a

total dose higher than 1,000 mg. showed signs of local irritation. A group of eighteen patients below one year of age (Table I) showed remarkably little reaction; five received more than three injections, and three patients more than ten injections. One patient, 16 days old, received twenty-two injections given at twelve-hour intervals for a total dose of 975 mg., and had slightly indurated buttocks when the treatment was completed.

Table XI. The Relation of Local Reaction to Patient's Age

PATIENT'S AGE (YR.)	NUMBER OF PATIENTS (81)	PER CENT OF PATIENTS WITH LOCAL REACTION	DEGREE OF LOCAL REACTION IN NUMBER OF PATIENTS		
			SEVERE	MODERATE	MILD
Under 1	18	5	–	–	1
1-5	31	26	2	3	4
5-13	32	22	1	2	4

Table XII. Therapeutic Effect in Forty-five Patients Treated With Intramuscular Terramycin

CLINICAL DIAGNOSIS	NUMBER OF PATIENTS TREATED	AVERAGE DOSE MG./KG./24 HR.	AVERAGE DURATION OF TREATMENT IN DAYS	RESULT		
				CURED	IMPROVED	UNIMPROVED
Acute bronchitis	2	9.2	3.2	2	–	–
Acute bronchiolitis	1	33.0	7.0	1	–	–
Bronchopneumonia	9	12.5	5.0	8	–	1
Pulmonary atelectasis	1	12.5	3.0	1	–	–
Acute pharyngitis	7	9.2	3.0	7	–	–
Acute tonsillitis	11	9.8	3.4	10	–	1
Acute otitis media	3	16.6	3.7	3	–	–
Cellulitis	2	12.5	3.0	2	–	–
Skin abscess	2	18.8	4.7	2	–	–
Vulvovaginitis	2	18.8	3.0	2	–	–
Pyelitis	2	28.0	7.0	2	–	–
Septicemia	1	25.0	11.0	1	–	–
Patent ductus endarteritis	1	60.0	4.0	–	–	1
Amoebic dysentery	1	25.0	7.0	–	1	–

THERAPEUTIC RESULTS

Forty-five patients were treated with intramuscular Terramycin. They were divided into age groups as follows: Thirteen were below 1 year of age, twenty-one between 1 and 5 years, and eleven between 5 and 13 years. Five patients who were treated with other antibiotics before admission to the hospital, and did not show clinical improvement, received intramuscular Terramycin and all responded well. The drug was injected at twelve-hour intervals in seventeen cases, at twenty-four-hour intervals in twenty-seven cases, and at six-hour intervals in one case. The dose ranged between 6 to 60 mg. per kilogram per twenty-four hours and was primarily calculated on a basis of age, type, and severity of illness. In 70 per cent of the patients, the dose did not exceed 12½ mg. per kilogram per twenty-four hours. The following results were obtained: Forty-one patients were cured, three did not respond to treatment, and one showed slight clinical improvement. Of the three patients who did not improve the first child had acute tonsillitis due to *Hemophilus influenzae;* the second, bronchopneumonia due to *Staph. aureus* hemolyticus and the third had patent

ductus endarteritis also caused by *Staph. aureus* hemolyticus. The sensitivity test in all of them showed resistance to Terramycin. A patient with amoebic dysentery received a dose of 25 mg. per kilogram per twenty-four hours for seven days. Slight clinical improvement was noticed as evidenced by reduction of the number of stools from five to three daily, absence of mucus, and better consistency of stools. This patient subsequently received oral Terramycin 50 mg. per kilogram per twenty-four hours for seven days, and as a result no amoebae were detected in five stool specimens.

Table XII illustrates the number of patients with different clinical conditions, the average dose in milligrams per kilogram per twenty-four hours, the average duration of treatment, and the therapeutic results.

Pulmonary Infections.—Two cases of acute bronchitis, one caused by pneumococcus and one by *Staph. aureus hemolyticus*, were cured after three days of treatment. A patient, 2 months of age, who had an acute pneumococcal bronchiolitis, was desperately ill on admission. The temperature was normal twelve hours after the Terramycin treatment was started, the substernal retractions subsided, and cyanosis disappeared. Eight patients with bronchopneumonia were cured. Four had pure pneumococcal and four mixed bacterial pneumonias, in which pneumococcus, *Staph. aureus* hemolyticus, *H. influenzae*, *E. coli*, and *Aerobacter aerogenes* were isolated from the sputum or pharyngeal secretions. In all cases the clinical diagnosis was confirmed by x-ray study. The response was excellent as manifested by improvement of clinical appearance and fall of temperature to normal in one day in five cases, and in two days in three cases. Terramycin was given for three days prophylactically to a premature infant weighing 1½ kilograms who had pulmonary atelectasis. No infection occurred and there was no local reaction.

Other Respiratory Tract Infections.—Seventeen patients with acute pharyngitis and tonsillitis showed good response to therapy with rapid subsidence of temperature from 102° to 105° F. to normal. The average dose in milligrams per kilogram per twenty-four hours did not exceed 10 mg. The organisms recovered from the pharynx were pneumococcus, *Staph. aureus* hemolyticus, *H. influenzae*, *Proteus mirabilis*, and *Proteus morgagni*. In three cases of purulent otitis media there was a rapid improvement in the appearance of the tympanitic membranes. Cultures showed *Staph. aureus* hemolyticus in one case, pneumococcus and *Pro. morgagni* in a second, and pneumococcus and *Pro. vulgaris* in a third case. The total therapeutic dose was slightly higher than in the cases of pharyngitis or tonsillitis.

Cutaneous Infections.—Uniformly good results were obtained in the treatment of two patients with cellulitis caused by *Staph. aureus* hemolyticus and two superficial abscesses. In the one case of an abscess, *Staph. aureus* hemolyticus was isolated, and in the second case, an incision was not performed and organisms could not be isolated.

Infections of the Genitourinary Tract.—In two patients who had vulvovaginitis, one gonococcal and one pneumococcal, the vaginal discharge was minimal twenty-four hours after the beginning of treatment, and on the

second day no organisms were detected on vaginal smear. Satisfactory results were obtained in two cases of pyelitis, one caused by *Pr. vulgaris* and the other by *Staph. aureus* nonhemolyticus. In both cases, cultures were sterile on the sixth day of treatment.

Septicemia.—A 16-day-old infant was admitted to the hospital in moribund condition with a temperature of 95° F., hepatosplenomegaly, and an icteric index of 151. *E. coli* was recovered from the blood stream. A high penicillin and streptomycin dose was given for one day without clinical improvement. Twenty-four hours after the first Terramycin injection, the icteric index was 61, the temperature 98° F., and the patient was able to tolerate formula. The total dose given in this case was 975 mg.

COMMENT

Significant serum concentrations were obtained after intramuscular administration of Terramycin. A single dose of 3 mg. per kilogram produced a therapeutic level lasting twelve hours. By increasing the dose to 6, then 12½, and finally 25 mg. per kilogram, the mean serum levels at one, eight, twelve, and twenty-four hours were proportionately doubled, and lasted for twenty-four hours. The dose of 25 mg. per kilogram produced concentrations similar to that obtained by Hunt and associates[7] after intravenous administration of 6.6 mg. per kilogram of Terramycin. After doubling the 25 mg. dose to 50 mg., the serum concentration was increased threefold. The peak levels were reached one hour after injection, although there were five cases in which the eight-hour level was as high as the first hour or even exceeded it. As indicated by these reports, a dose of 6 mg. per kilogram gives blood levels equal to a single oral dose of 22 or 33 mg. per kilogram.

The absorption into the blood stream after injections of various dosages was very rapid, and in fifteen minutes a high therapeutic level was obtained, which demonstrates the fact that the intravenous route of administration is not essential.

The diffusion of Terramycin into the cerebrospinal fluid in two normal patients was poor, and the results were similar to those of Schoenbach and Bryer[3] and Herrell and associates.[5]

The therapeutic results in forty-five patients were very encouraging. Only four cases required other antibiotic therapy or other forms of treatment. Thirty per cent of our patients were cured with a dose of 6 mg. per kilogram per twenty-four hours, and 40 per cent with a dose of 12½ mg. per kilogram per twenty-four hours. Most of the patients belonging to the latter group were treated before the results of the serum levels were obtained, and we feel that they might have been cured with a lower dose.

Because most of the strains of pneumococcus, *Streptococcus pyogenes* Group A, *Staph. aureus* hemolyticus, *H. influenzae*, and *N. gonorrhoeae* are inhibited in vitro by concentration of Terramycin 0.06 to 0.3 μg per cubic centimeter,[9] a dose of 6 to 12 mg. per kilogram per twenty-four hours should be adequate in mild or moderately severe infections caused by these organisms. Urinary tract infections caused by gram-negative *E. coli* and *Pr. vulgaris* will require a dose of 25 mg. per kilogram per twenty-four hours or higher. Since higher Terramycin concentrations (25 to 50 mg. per kilo-

gram) may produce bactericidal effects, it is desirable that desperately ill patients should receive high concentrations at least for the critical period, and injections should be given at twelve-hour intervals. It was shown by Hobby and associates[3] in in vitro studies with a strain of hemolytic streptococcus that Terramycin was bacteriostatic in a concentration of 0.9 μg per cubic centimeter and bactericidal in a concentration of 1.9 μg per cubic centimeter. Further increase in the concentration produced more marked bactericidal effects.

In the administration of this preparation of Terramycin the possibility of local reaction has to be considered. In eighty-one patients who received injections, seventeen (20 per cent) patients had some degree of local irritation, but the majority of them (60 per cent) had only slight tenderness by palpation which persisted for no longer than one day. In order to reduce the incidence of local reactions, the injections should be given deeply into the gluteal muscles at twenty-four-hour intervals, alternating the buttocks, and the concentration used should be 100 mg. per cubic centimeter. A remarkably high number of infants and young children tolerated this drug very well. From our results we conclude that this intramuscular preparation will be of great help in the treatment of acute infections, particularly in infants and young children who cannot take the drug orally, also where intravenous administration presents technical difficulties.

SUMMARY

1. Serum and cerebrospinal Terramycin concentrations were determined in sixty-three infants and children who were on various dosage schedules, and the results of 240 bio-assays are reported.

2. Therapeutic response in forty-five patients presenting fourteen different clinical conditions is reported.

3. The influence of various factors upon the incidence of local reactions following intramuscular administration of Terramycin is analyzed.

4. Dosage schedules for the proper administration of intramuscular Terramycin in the pediatric age group are advised.

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REFERENCES

1. Kane, J. H., Finlay, A. C., and Sobin, B. A.: Antimicrobial Agents From Natural Sources, Ann. New York Acad. Sc. 53: 226, 1950.
2. Hobby, Gladys, and others: Antimicrobial Action of Terramycin in Vitro and Vivo, Proc. Soc. Exper. Biol. & Med. 73: 503, 1950.
3. Schoenbach, E. B., and Bryer, M. S.: Pharmacology of Terramycin in Animals and Man With Reference of Its Clinical Trials, Ann. New York Acad. Sc. 53: 245, 1950.
4. Welch, H.: Absorption, Excretion, and Distribution of Terramycin, Ann. New York Acad. Sc. 53: 251, 1950.
5. Herrell, W. E., Heilman, F. R., Wellman, W. E., and Bartholomew, L. G.: Terramycin; Some Pharmacological and Clinical Observations, Proc. Staff Meet., Mayo Clin. 25: 183, 1950.
6. Sayer, R. J., Michel, J. C., Moll, F. C., and Kirby, W. M. M.: Terramycin: Clinical, Pharmacologic and Bacteriologic Studies, Am. J. Med. Sc. 221: 256, 1951.
7. Hunt, A. D., Jr., Kelly, R. S., Coriell, L. L., Murphy, L. M., Tashman, S. G., and Stevens, C.: Studies on Absorption and Distribution of Terramycin in Children, J. PEDIAT. 40: 607, 1952.
8. Kersey, R. C.: A Turbidimetric Assay for Terramycin, J. Am. Pharmacol. A. 39: 252, 1950.
9. Welch, H., Randall, W. A., Reedy, R. J., and Kremer, J.: Bacterial Spectrum of Erythromycin, Magnamycin, Chloramphenicol, Aureomycin, and Terramycin, Antibiotics & Chemother. 2: 643, 1952.

THE TREATMENT OF ERYTHROBLASTOSIS FETALIS WITH REPLACEMENT TRANSFUSION

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THE concept of exchanging the blood of an affected infant for that of a healthy individual is not new.[1] However, this procedure has been used in the treatment of erythroblastosis fetalis only recently.[2-8] The rationale for this form of therapy is based on the theory that the pathology of hemolytic disease of the newborn results from reaction between an antigen (the Rh-positive infant's red blood cells) and an antibody (Rh antibody derived from the Rh-negative mother's serum across the placental barrier).[9, 10] It is, therefore, logical to assume that any treatment which will remove quantities of antibody and products of red blood cell destruction will greatly benefit the affected infant. At present this can best be accomplished by replacement therapy.

This presentation will attempt to demonstrate the therapeutic benefits of exchange transfusion and to clarify the criteria for the choice of this method of treament. In addition it will be demonstrated that replacement transfusion must be done within twenty-four hours after birth to insure the best results.

INDICATIONS

Because of the availability of newer laboratory methods, many patients with mild cases of erythroblastosis fetalis who require little or no treatment are now diagnosed. At birth, these infants are indistinguishable from many affected ones who appear quite normal at birth, but who, if not promptly treated, will become severely ill during the ensuing twenty-four to seventy-two hours. Therefore the choice of cases for treatment with replacement transfusion is of major importance. The factors involved in reaching a decision as to therapy are as follows:

Maternal Antibody Titer.—There is a rough correlation between the height of the maternal antibody titer and the severity of involvement of the offspring. However, this factor is of relatively poor prognostic value in any single case. Severe involvement may occur despite low maternal antibody titers.

Coombs Test on Cord Red Blood Cells.[12]—This is a sensitive test for the detection of antibody fixed to the red blood cell. An accurately done negative Coombs test effectively eliminates the diagnosis of erythroblastosis fetalis due to the Rh factor. However, the mere presence of a positive Coombs test does not indicate that exchange transfusion is necessary.

Cord Blood Hemoglobin Level.—Mollison and Cutbush[13] have demonstrated that in their group of cases, if the cord hemoglobin was above 15.5 grams per cent, no replacement therapy was required. A cord hemoglobin level below 15.5 grams per cent is considered

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by them to be an indication for immediate exchange transfusion.

Blood Count.—Repeated determinations on the infant's blood which reveal progressively falling hemoglobin levels, or rising reticulocytes, normoblast counts or rising white blood cell counts in the peripheral blood, supply evidence of active hemolysis and an indication for radical therapy.

Clinical Findings.—The presence or development of pallor, edema, jaundice, or hepatosplenomegaly during the first twenty-four hours of life are signs of severe involvement necessitating replacement therapy.

Family History.—Any infant whose family history includes a sibling who had erythroblastosis fetalis is treated with exchange transfusions if the Coombs test on cord blood is positive.

PROCEDURE[11]

Rh determinations and blood groupings are done on all pregnant women. All Rh-negative mothers are tested for sensitization to blood antigens. Repeated titrations are done on sensitized women.

A complete blood count and physical examination are done on the infant at birth. Complete blood count, Coombs test, blood type, and Rh are done on cord oxalated blood.

It is required that the hematologist and the pediatrician be available at the delivery of all potentially affected infants.

REPLACEMENT TRANSFUSION PROCEDURE

1. The operation is done usually within the first eight hours of life, and rarely after twenty-four hours.

2. The procedure is done in an operating room on the obstetrical floor so that the infant may be returned to the regular newborn nursery rather than to the pediatric floor.

3. Gastric aspiration is done to prevent vomiting and aspiration pneumonia.

4. Polyethylene tubing is inserted into the umbilical vein. Both the removal and instillation of fresh blood are done via the umbilical catheter.

5. Type specific fresh Rh-negative whole blood, less than thirty-six hours old, is used exclusively without regard to sex of donor.

6. The initial step in this procedure is the withdrawal of 50 c.c. of the infant's blood to ensure an efficient exchange.[13] This step may be modified if the patient's hemoglobin is so low as to require an initial transfusion to help withstand the operation. Subsequently, blood is exchanged in units of 20 to 50 c.c.

7. The total amount of blood exchanged has been 50 to 60 c.c. per pound of body weight.

8. The entire procedure may be done in a heated crib with the administration of oxygen when indicated.

9. One hundred milligrams of calcium gluconate is injected for each 100 to 150 c.c. of blood exchanged and 500 mg. of calcium gluconate after the exchange is completed.

10. Postoperatively, the infant is maintained on adequate doses of penicillin for three days.

11. Careful attention is paid to the hydration of the infants postoperatively. Parenteral fluids are used when indicated.

12. Subsequent transfusions are given when required. Arbitrarily, 2,500,000 red blood cells per cubic milllimeter and 7½ grams hemo-

globin per cent have been set as the level at which additional transfusions have been given.

RESULTS

One hundred six cases of erythroblastosis fetalis have been treated with replacement transfusion. There were seven deaths, giving an over-all mortality of 6.6 per cent. Before the results of this series can be evaluated, it must be specified which types of cases have been treated. A recent report by Dr. C. J. Molony has outlined a series of criteria for evaluating any single case.[15] (See Table I.) According to these criteria, 80 per cent of this series were severe cases, 15 per cent moderate cases, and 5 per cent mild cases. (Of the seven patients who died, five were classified as severe, and two as moderate.) (See Table II.)

It has been noted by various authors that infants who had previously ill siblings have a relatively low survival rate.[16] Included in this series are twenty-five infants with a positive family history. Fourteen of the infants were severely affected, nine were moderately affected, and two were mild. (See Table III.)

It will also be noted that sixteen of the twenty-four infants were delivered following induction of labor or cesarean section (for obstetrical indications only) two to three weeks prior to term. Despite this, only two infants weighed less than 5½ pounds at birth.

Maternal blocking antibody titers were usually above 1:16; however, they varied from 1:2 to 1:512. The data in Table III emphasize the impossibility of predicting the severity of the disease in the infant from maternal antibody titers in any single case. Of the nine infants whose mothers had low titers (below 1:16), four were severe, three were moderate, and two were mild. Sixteen of the twenty-five infants had been preceded by one or more stillborns or siblings who had died of erythroblastosis fetalis. Since all of the above infants survived, it appears from these data that when treated with exchange transfusion, the survival rate among these infants is no worse than in the general group of cases.

All infants treated with exchange transfusions became jaundiced postoperatively. However, only two were

TABLE I. METHOD OF DETERMINING SEVERITY OF DISEASE*

Severity of disease in individual proved cases of erythroblastosis is based on one point each for:

a. Jaundice in first few hours.
b. Liver enlarged and spleen easily palpable at first examination.
c. Anemia below 12.0 Gm. hemoglobin at birth.
d. Normoblasts greater than 25 per 100 white blood cells at first examination.
e. Moderate or strong plus Coombs test.
f. Cord icterus index above 50 units.
g. Previously affected sibling.
h. Evident severe case with cyanosis and rapid irregular respirations not due to atelectasis at birth.

A score of (1) or (2) = mild case.
A score of (3) or (4) = moderate case.
A score of (5) or higher = severe case.

*Molony, C. J.: Treatment of Erythroblastosis, Pediatrics 5: 1008, 1950.

TABLE II

MOTHER			INFANT		
CASE NO.	PREVIOUS PREGNANCY OR BLOOD TRANSFUSION	ANTIBODY TITER	RACE, SEX, BIRTH WEIGHT	COURSE	NECROPSY
12	None	Bl. 1:16	Negro Female 6 lb. 6 oz.	Hb. 7.5 Gm., RBC 2 M, 71% normoblasts, jaundice, cyanotic, liver and spleen enlarged 2 cm. below costal margin. Expired 2 hr. postoperatively, with generalized edema and râles	Edema, esophagitis, gastritis, venous congestion, degeneration of liver, kernicterus
17	2 children living and well (female Rh-negative donor used with plasma removed)	Bl. 1:16	White Female 6 lb.	Hb. 10 Gm., RBC 2.9 M, 10% normoblasts, liver and spleen enlarged 2 cm. below costal margin. Jaundiced in 2 hr. Expired on second day. Hb. dropped from 17 to 9 Gm.	Marked jaundice, kernicterus, generalized edema
51	3 spontaneous abortions at about fifth month	Bl. 1:32	White Female 4 lb. 6 oz.	Hb. 5 Gm., RBC 1.1 M, 200 nucleated red cells per 100 white cells, pallor, jaundice, hepatosplenomegaly at birth. Infant went into collapse during exchange transfusion (300 c.c. exch.). Rallied and seemed well but suddenly expired at 20 hr. after birth	Prematurity. Enlarged liver and spleen with increased hematopoiesis, marked congenital atelectasis
101	2 children living and well, 2 abortions	Bl. 1:4	Negro Male 6 lb. 6 oz.	Hb. 123% dropped to 81%, Coombs 3 plus, RBC 4.83, WBC 14,600. Expired within 24 hr. due to pulmonary complications from aspiration	Pulmonary atelectasis, erythroblastosis fetalis
80	1 living and well	Bl. 1:8	White Male 6 lb. 2 oz.	Hb. 6 Gm., RBC 1.340 M, WBC 97 M, pallor, edematous, partially macerated. Died in middle of replacement transfusion	Partially macerated, fetal hydrops
70	1 living and well	Bl. 1:64	White Male 7 lb. 9 oz.	Coombs positive, O Rh pos., liver and spleen enlarged, markedly jaundiced, lethargic, prognosis poor, expired on third day	Lower nephron nephrosis, erythroblastosis fetalis, kernicterus

TABLE II—CONT'D

MOTHER			INFANT		
CASE NO.	PREVIOUS PREGNANCY OR BLOOD TRANSFUSION	ANTIBODY TITER	RACE, SEX, BIRTH WEIGHT	COURSE	NECROPSY
40	1 living and well. 2 died of erythroblastosis fetalis	Bl. 1:16	White Female 7 lb. 6 oz.	Delivered by cesarean section, O Rh pos. Coombs 4 plus, jaundiced, liver and spleen palpable one fingerbreadth below costal margin. Hemoglobin 16.5 Gm. Exchange transfusion done 4 hr. after birth. Hemoglobin remained around 16 Gm. Infant seemed to do well. Suddenly developed rapid respiration on fourth day, weak, fed poorly. Expired fifth day	Bronchopneumonia both lower lobes. Erythroblastosis fetalis. Retroperitoneal edema ascites (min.). Congestion of brain

severely ill. Neither of these was handled as described above, but were transfused on the pediatric wards using a different technique. Their extended illness was due to secondary infection contracted while on the hospital ward. With few exceptions, these infants have been able to leave the hospital with their mothers; the average hospital stay has been about seven days.

A substantial number of children required subsequent blood transfusions at varying intervals, although more than 50 per cent of them required no supplementary transfusions. At 7 to 8 weeks the infant's hemoglobin may drop as low as 7 to 8 grams. However, by the end of three months, all the children were beginning to show a steady rise in hemoglobin and red count.

Follow-up studies have not extended beyond three years. However, to date, only one known case of kernicterus has been seen in the surviving infants in this series.

Examination of our results (with a mortality of 6.6 per cent) as compared with other large series similarly handled in many ways reveals that our mortality rates are extremely low. This may be explained by the fact that we have been fortunate enough to handle all of our cases within twenty-four hours after birth (and most within eight hours after birth).

DISCUSSION

It has been demonstrated that the mortality rate in erythroblastosis fetalis can be lowered by the use of exchange transfusion. But it is obvious that not every case that can be diagnosed by present-day laboratory methods requires such radical treatment. Since relatively severe damage to the infant may occur quickly, an early decision as to method of therapy must be made. Various criteria for use of replacement transfusion have been advocated. The criteria of greatest value in our hands have proved to be as follows:

TABLE III. MOTHERS WITH POOR OBSTETRICAL AND CLINICAL HISTORIES WHOSE INFANTS WERE TREATED WITH EXCHANGE TRANSFUSIONS*

CASE NO.	BIRTH WT. (LB. OZ.)	CLASSIFICATION	PREVIOUS PREGNANCY	PREVIOUS TRANSFUSIONS	ANTIBODY TITER	INDUCTION
2	8-10	Severe	3 siblings living and well 1 stillborn 1 spon. abortion	None	Bl. 1:128	38 wk.
3	4- 8	Severe	1 sibling living and well 2 siblings jaundiced 1 stillborn	None	Bl. 1:32	38 wk.
5	7- 8	Severe	3 siblings living and well 2 siblings jaundiced 1 anemic	None	Bl. 1:512 Agg. 1:4	None
6	6- 3	Severe	3 siblings living and well 3 siblings jaundiced 1 sibling anemic	None	Bl. 1:64	None
9	6- 8½	Moderate	8 siblings living and well 1 miscarriage	None	Bl. 1:128	38 wk.
10	6-13	Moderate	2 siblings living and well 3 siblings jaundiced	None	Bl. 1:32	38 wk.
11	7- 6	Moderate	1 sibling living and well 1 stillborn	None	Bl. 1:16	None
16	5-10	Severe	2 siblings living and well 2 stillborn	None	Bl. 1:8 Agg. 1:2	37 wk.
21	6-11	Moderate	1 sibling living and well 2 spon. abortion	None	Bl. 1:8	37 wk.
22	7-11	Moderate	1 sibling living and well	One	Bl. 1:16	Repeat cesarean section 38 wk.
24	6-10	Severe	2 siblings living and well 1 miscarriage 1 expired jaundiced	None	Bl. 1:8	38 wk.
25	5-14	Mild	Next child of Case 24	None	Bl. 1:4	38 wk.
26	8-16	Severe	2 siblings living and well 1 miscarriage	None	Bl. 1:32	38 wk.
27	7- 4	Severe	1 sibling living and well 2 stillborn	None	Bl. 1:32	Repeat cesarean section at 37 wk.
29	-	Severe	1 sibling living and well 2 expired 3 days after birth	None	Bl. 1:4	37 wk.
30	6-15	Severe	1 sibling living and well 1 stillborn 1 expired 12 hr.	None	Bl. 1:16	Repeat cesarean section 37 wk.
31	6- 1	Severe	2 siblings living and well 1 sibling jaundiced	None	Bl. 1:512	37 wk.
56	7- 2	Mild	1 sibling living and well 1 sibling expired 3 wk.	None	Bl. 1:2	None
78	7- 0	Severe	7 siblings living and well 2 siblings expired jaundiced	None	No titer	None
81	6- 0	Severe	1 sibling living and well 1 sibling expired jaundiced	None	Bl. 1:2	None
82	6- 8	Severe	2 siblings living and well 1 stillborn (hydrops)	None	Bl. 1:32	None
91	8- 0	Moderate	3 siblings living and well 1 sib. with E. F. recovered after multiple transfusions	None	Bl. 1:2	None
94	6- 8	Moderate	3 siblings expired (last 2 jaundiced, expired during first 24 hr.)	None	Bl. 1:2	None
95	7- 0	Moderate	1 sibling living and well 3 siblings expired at birth	None	Bl. 1:32	None
103	4- 0	Moderate	1 sibling living and well 2 stillborn at 30 weeks' gestation	None	Bl. 1:64	Repeat cesarean section at 36 wk.

*All of the above infants survived without residua.

1. Positive Coombs test on cord red blood cells.

2. Cord blood hemoglobin level below 15.5 grams.

3. Development of physical findings (i.e., jaundice, pallor, hepatosplenomegaly) within the first twenty-four hours of life.

4. Progressively developing laboratory evidence of hemolysis (falling hemoglobin, increasing reticulocytosis or erythroblastosis) within the first twenty-four hours of life. In babies where conservative therapy is decided upon, the following tests are done every four hours: hemoglobin, reticulocyte count, and white blood cell count.

The finding of a positive Coombs test plus any one of the above listed abnormalities we believe is an indication for immediate exchange transfusion.

In those infants born of mothers who had given birth to previously affected infants, induction of labor has been advocated after the thirty-eighth week of gestation. In addition, replacement transfusion has been done immediately on all infants with a positive family history if the Coombs test is positive.

The reasons why exchange transfusion seems to be the most logical treatment, not only theoretically but practically, are as follows:

1. Elimination of large amounts of circulating antibody.

2. Elimination of many of the affected red cells.

3. Replacement with an Rh-negative cell that is not affected by any remaining antibody.

4. Possible mobilization of fixed tissue antibody (if this exists).

5. Overloading the circulation is minimized.

6. Elimination in many cases of the necessity for repeated transfusions.

While it is obviously impossible to determine what might have happened to any single infant without exchange transfusion, a series of twelve infants who fulfilled the criteria but were not exsanguinated will be presented. The reasons for conservative therapy were either erroneous diagnosis or denial of permission for the procedure. (See Table IV).

It can be seen that six patients died, a mortality rate of 50 per cent. Five others were severely ill, but recovered after prolonged treatment with multiple transfusions; one was mildly affected and recovered with therapy. Three of the patients who died showed post-mortem findings of kernicterus. From these results it would seem obvious that exchange transfusion is of very definite value.

In attempting to evaluate the results, there are other factors worthy of note.

1. Every case is seen and handled from birth by a team consisting of a hematologist and a pediatrician. The decision for exchange is made as soon as the facts become available. In almost every case, the operation was performed within twenty-four hours after birth. Type-specific Rh-negative blood and the necessary transfusion equipment are ready for use.

2. Postoperatively it has been arranged that the infant be returned to the regular newborn nursery rather than to the pediatric ward where danger of secondary infection is greater.

TABLE IV. INFANTS TREATED CONSERVATIVELY DESPITE INDICATION FOR REPLACEMENT TRANSFUSION

RACE SEX BIRTH WT.	PAST HISTORY	MATERNAL ANTIBODY TITER	COOMBS	COURSE	POST-MORTEM FINDINGS
W. M. 7 lb.	1 sib. L. & W.	Agg. 0 Block. 1:16	4 plus	Jaundice and hepatosplenomegaly. Diagnosis made at about 36 hr. Expired at 72 hr. despite multiple transfusions	No post-mortem examination
W. M. 5 lb. 14 oz.	2 sib. L. &. W.	Agg. 1:32 Block. 1:128	4 plus	Pallor, jaundice, and anemia at birth. Permission for exchange transfusion refused by parents. Expired at 72 hr. despite multiple transfusions	Jaundice. Hepatosplenomegaly with extramedullary hematopoiesis. Diffuse hemorrhage in lungs, stomach and bladder
W. M. 6 lb. 9 oz.	1 sib. L. & W.	Agg. 0 Block. 1:128	4 plus	Anemia, jaundice, hepatosplenomegaly. Diagnosis missed for 48 hr. Expired 70 hr. despite multiple transfusions	Jaundice. Hepatosplenomegaly with extramedullary hematopoiesis. Kernicterus
W. M. 5 lb. 11 oz.	1 sib. L. & W. 3 stillborn	Agg. 0 Block. 1:32	Not done	Anemia, jaundice, hepatosplenomegaly. Diagnosis missed for over 48 hr. Gradually recovered with multiple transfusions. Hospital stay 30 da.	
W. M. 5 lb. 5 oz.	1 sib. L. & W.	Agg. 1:32 Block. 1:128	3 plus	Jaundice and progressive anemia. Diagnosis missed for over 48 hr. Expired 60 hr. despite several transfusions	Jaundice, extramedullary hematopoiesis. Slightly enlarged liver and spleen. Pulmonary congestion and edema. Severe kernicterus
N. F. 5 lb. 10 oz.	1 sib. L. & W.	Agg. 0 Block. 1:64	Not done	Jaundice, anemia, hepatosplenomegaly. Diagnosis missed for over 48 hr. Expired 72 hr. despite transfusions	Jaundice, hepatosplenomegaly with extramedullary hematopoiesis. Severe kernicterus
N. F. 6 lb.	1 sib. L. & W. 1 sib. with mild E. F.	Agg. 1:2 Block. 1:128	3 plus	Slight jaundice and progressive anemia. Diagnosis missed for over 48 hr. Recovered after multiple transfusions. Hospital stay 21 da.	

TABLE IV—CONT'D

RACE SEX BIRTH WT.	PAST HISTORY	MATERNAL (NTIBODY TITER	COOMBS	COURSE	POST-MORTEM FINDINGS
W. M. 6 lb.	2 sib. L. & W. 1 stillborn	Agg. 1:16 Block. 1:512	Not done	Transferred from another hospital at age 5 da., with mild jaundice and a history of progressive anemia. Recovered after multiple transfusions over 1-month period	
N. F. 7 lb. 9 oz.	2 sib. L. & W.	Agg. 0 Block. 1:64	Not done	Severe jaundice, hepatosplenomegaly, and increasing anemia. Diagnosis missed for 48 hr. Recovered after multiple transfusions over a 1-month period	
W. F. 6 lb.	2 sib. L. & W.	Agg. 0 Block. 1:1	4 plus	Slight jaundice. Mild anemia within 24 hr. Permission for replacement therapy denied. Expired at 75 hr. despite multiple transfusions	Jaundice. Hepatosplenomegaly with extramedullary hematopoiesis. Kernicterus
N. M. 6 lb. 1 oz.	Primipara (mother transfused 4 yr. previously)	Agg. 0 Block. 1:16	Not done	Jaundice noted at 48 hr. Infant recovered after multiple transfusions over 21-day period	
N. F. 9 lb. 6 oz.	1 sib. L. & W. 1 stillborn	Ag. 0 Block. 1:512	Not done	Jaundice noted at 48 hr. Diagnosis missed. Infant recovered without therapy. Discharged in good condition at age 1 wk.	

3. Careful attention is paid to general pediatric care postoperatively. Heated cribs and oxygen are used as indicated. All infants are treated with antibiotics and vitamin K. Parenteral fluids are used as needed to maintain fluid and electrolyte balance.

Some of these children might have survived without exchange transfusion, but the difficulty in determining which children will be severely affected demands radical treatment early. Conservative handling with watchful waiting and multiple transfusions has reduced mortality rates to 20 to 50 per cent. Exchange transfusions done after twenty-four to forty-eight hours may not be effective, since irreparable damage may already have been done. Therefore, any infant with a positive Coombs test, who shows signs of hemolysis or physical findings of erythroblastosis fetalis, should be afforded maximum therapy promptly.

SUMMARY

One hundred six cases of erythroblastosis fetalis have been treated with exchange transfusion. There were seven deaths, giving an over-all mortality of 6.6 per cent. The indications for early exchange transfusion are enumerated. The practical and theoretical advantages of exchange transfusion are discussed.

REFERENCES

1. Hart, A. P.: Canad. M. A. J. **15:** 1008, 1925.
2. Polayes, S.: Quoted by Wallerstein; Am. J. Dis. Child. **73:** 19, 1947.
3. Wallerstein, H.: Blood, Special Issue, Nov. 2, p. 170, 1948.
4. Diamond, L. K.: Pediatrics **2:** 250, 1948.
5. Wiener, A. S., and Wexler, I. B.: Blood **4:** 1, 1949.
6. Wiener, A. S., and Wexler, I. B.: Postgrad. Med. 1-1950.
7. Vaughan, V. C., III, Allen, F. H., Jr., and Diamond, L. K.: Pediatrics **6:** 173, 1950.
8. Sacks, M. S., Spurling, C. C., Bross, I. D. S., and Jahn, E. F.: Pediatrics **6:** 772, 1950.
9. Levine, P., and Stetson, R.: J. A. M. A. **113:** 126, 1939.
10. Levine, P.: J. PEDIAT. **23:** 656, 1943.
11. Ginsberg, V., and Feldman, F.: Am. J. Obst. & Gynec. **59:** 618, 1950.
12. Coombs, R. R. A., Mourant, A. E., and Race, R. R.: Brit. J. Exper. Path. **26:** 255, 1945.
13. Mollison, P. L., and Cutbush, Marie: Blood **6:** 777, 1951.
14. Vogel, P.: Bull. New York Acad. Med. **25:** 261, 1949.
15. Molony, C. J.: Pediatrics **5:** 1008, 1950.
16. Potter, Edith: Pediatrics **2:** 369, 1948.
17. Brancato, J. B.: Am. J. Dis. Child. **80:** 1, 1950.

CHYLOUS ASCITES

Report of a Case With Recovery and Survival After Fourteen Years

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THE finding of free chyle in the peritoneal cavity is extremely rare in early life.[1] At least two cases of congenital chylous ascites have been reported.[2, 3] Kessel[1] reported a case of chylous ascites in an 11-week-old female infant, and Kerr[4] reported a case in an infant 16 days of age. In a review of the literature Lee and Young[5] found twenty-seven cases in children up to 15 years of age and added two (siblings) of their own.

Chylous ascites is often associated with chylothorax. Yater[6] found that the two conditions were present in one-half of the cases of chylothorax that he reviewed.

CASE REPORT

J. D., a 6-month-old Negro male (Fig. 1), was admitted to the pediatric service on Sept. 1, 1939, with a chief complaint, as given by the mother, of progressive, generalized, and symmetrical abdominal enlargement since the age of 2 months. At the onset the abdominal enlargement was associated with transient vomiting which later disappeared. The stools were said to have been normal, numbered one to three per day and neither diarrhea nor constipation was a feature.

The infant, who was delivered at term of a normal labor, was well until the onset of the present illness. The parents appeared to be in normal health.

The physical examination revealed a well-developed, poorly-nourished infant who weighed 11 pounds 4 ounces, with a crown-to-heel measurement of 23.7 inches. The circumference of the head, chest, and abdomen measured 15.8, 14.4, and 17 inches, respectively. Physical findings were essentially normal except for the abdomen which presented dilated superficial veins and was distended symmetrically. It was tense and no masses were palpable. The percussion note was flat and a fluid wave was elicited.

On admission the h e m o g r a m showed 3.8 million red blood cells and 5,600 white blood cells with a normal differential count. The intradermal tuberculin test and the serologic test for syphilis were both negative. Roentgenologic studies of the abdomen showed marked distention of the abdomen with elevation of the diaphragm on both sides. Hirschsprung's disease was excluded by barium studies of the large intestine. Similarly, lesions of the upper gastrointestinal tract were ruled out. Roentgenogram of the chest was negative except for bilateral elevation of the diaphragm.

On the fourth hospital day a diagnostic paracentesis was performed, at a level of one centimeter directly below the umbilicus, with removal of 8 c.c. of milky fluid. The same type of fluid was removed on eight subsequent occasions by paracenteses extending over a period between the fourth and seventy-first days of hospitalization. Total fluid removed was approximately 3,140 c.c. with an average of 392.5 c.c. per puncture. The largest amount that was removed at any one time was 529 c.c.

This white fluid, which was visibly indistinguishable from milk, had no

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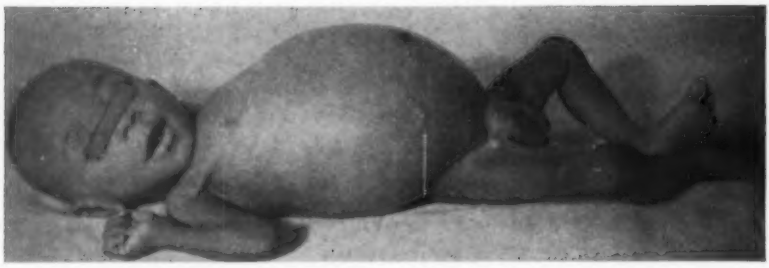

Fig. 1.—Patient as he appeared during early period of hospitalization with marked abdominal enlargement due to ascites.

Fig. 2.—Patient after recovery. No evidence of abdominal enlargement.

odor. The specific gravity was 1.020. It was not visibly coagulated with heat but there was precipitation with nitric acid. Chemical analysis revealed the following composition: fat, 4 grams per 100 c.c.; nonprotein nitrogen, 20 mg. per 100 c.c.; total nitrogen, 730 mg. per 100 c.c.; protein nitrogen, 710 mg. per 100 c.c.; protein (N × 6.25), 4.3 grams per 100 c.c.

Microscopically the fluid showed fat globules when stained with Sudan III dye. Bacteriologic studies on the sterile fluid revealed no bacteriostatic or bacteriocidal activity. On the basis of the above findings it was reasonable to accept the peritoneal fluid as chyle.

The patient was placed on an Olac formula and parenteral electrolyte fluids were administered to correct the dehydration. His condition improved slowly although there was a period when he appeared to be losing ground. By the one hundred sixty-eighth day of hospitalization there was no evidence of the ascites (Fig. 2). He was discharged at the age of 12 months in good condition.

On July 8, 1953, nearly fourteen years after the beginning of his hospitalization, the patient was found to be living and well. He had just graduated from the eighth grade and had had no recurrences of his ascites. The patient had been lost to follow-up before this time.

DISCUSSION

Nelson[7] lists the causes of true chylous ascites as anomalies, injuries, and obstructions of the thoracic duct. He believes that the cases which appear at birth, or shortly thereafter,

are due to anomalies. He further states that the products of the degeneration of inflammatory tissue in chronic tuberculous and nontuberculous peritonitis may result in peritoneal fluid that has an appearance similar to that observed in true chylous ascites. Peritoneal carcinoma may also result in milky peritoneal effusion.[1] The case presented here was probably due to a congenital anomaly or birth injury.

Obstruction of the thoracic duct can result from several conditions. These include enlarged mediastinal lymph nodes and tumors, parasitic infestations of the duct, direct pressure caused by an enlarged heart, tumors of the pancreas, stenosis of the duct following invasion by neoplastic or tuberculous growths, aneurysm of the aortic arch, surgical ligature, thrombosis of the left subclavian vein at the area of joining with the thoracic duct.[8, 9]

The obstruction results in increased pressure in the ductal system with a resulting dilatation of the thoracic lymphatic vessels.[8] Although a collateral circulation may be established, some leakage occurs into the pleural cavity and/or the peritoneal cavity. The result is chylothorax, chylous ascites, or both. In cases of trauma, chylous ascites may occur due to rupture of the thoracic duct, the cisterna chyli, or other lymphatic vessels.[8] The chances of an effusion developing are less if the obstruction develops slowly.[10]

Lee's[11] experiments throw some doubt on the obstruction theory. He completely ligated the thoracic ducts of cats and came to the conclusion that the thoracic duct was not essential to the life of these animals because collateral channels developed and no chylothorax or chylous ascites was evident. Other workers,[12] however, believe that his work has not eliminated the possibility of producing chylous ascites by compression of the main thoracic duct and collateral lymph channels.

Venous-peritoneal anastomoses and other abdominal drainage procedures have been performed for the successful correction of this condition.[3, 13, 14] This type of procedure (Routte's operation[3]) was considered for the case reported here; however, operative plans were abandoned when the condition responded satisfactorily to conservative therapy (paracenteses). Surgery has also been successful in the removal of the mechanical causes of obstruction.[15]

In Lee and Young's[5] review of twenty-nine reported cases, sixteen were treated conservatively and thirteen of these recovered. The conservative management consists of a low fat and high protein diet, paracenteses together with adequate quantities of the fat-soluble vitamins administered orally in aqueous dispersion. It has been indicated by studies on vitamin A absorption, that fat-soluble vitamins in aqueous dispersion are absorbed in appreciable quantities into the blood stream in cases of chylous ascites.[16]

SUMMARY

A case of chylous ascites is presented in a Negro infant whose abdominal enlargement was first observed by the parent at the age of 2 months. Therapy consisted of periodic abdominal paracentesis for removal of fluid, Olac formula, parenteral fluids, and oral vitamins. The

chylous ascites gradually but completely disappeared clinically by the end of the first year of life. Approximately fourteen years after treatment the child is normal and shows no evidence whatsoever of the old infantile complaint. The exact mechanism of the condition in this case was not determined but represented a probable congenital anomaly or birth injury involving the abdominal lymphatic system. General aspects of etiology and therapy are discussed.

Dr. Alonzo deG. Smith was responsible for the medical management of this case. Dr. Vernon A. Wilkerson performed the chemical analysis, and Dr. H. A. Poindexter carried out bacteriologic studies on the chylous fluid.

REFERENCES

1. Kessel, I.: Chylous Ascites in Infancy, Arch. Dis. Childhood **27**: 79, 1952.
2. Boston, L. N.: Chylous Ascites With Eosinophilia, J. A. M. A. **44**: 513, 1905.
3. Wegner, E. S.: Congenital Chylous Ascites; Apparently Cured by Routte's Operation (Venous Peritoneal Anastomoses), Am. J. Dis. Child. **47**: 586, 1934.
4. Kerr, Le G.: Chylous Ascites in Infant 16 Days Old, New York J. Med. **9**: 14, 1909.
5. Lee, C. H., and Young, J. R.: Chylous Ascites in Siblings, J. PEDIAT. **42**: 83, 1953.
6. Yater, W. M.: Non-traumatic Chylothorax and Chyloperitoneum; Review and Report of a Case Due to Carcinomatous Thrombo-Angiitis Obliterans of the Thoracic Duct and Upper Great Veins, Ann. Int. Med. **9**: 600, 1935.
7. Nelson, W. E.: Mitchell-Nelson Textbook of Pediatrics, ed. 5, Philadelphia, 1950, W. B. Saunders Co., p. 853.
8. Curtis, G. M.: in Christopher's Textbook of Surgery, ed. 5, Philadelphia, W. B. Saunders Co., pp. 671-672.
9. Bergenfreid, A., and Fanta, E.: Ascitis Quilosa de Origen Hidatidico, Bol. Informaciones Parasitarias Chilenas (Santiago) **7**: 43, 1952.
10. Palken, M., and Weller, R. W.: Chylothorax and Chyloperitoneum; Report of a Case Occurring After Embolism of Left Subclavian Vein With Thoracic Duct Obstruction, J. A. M. A. **147**: 566, 1951.
11. Lee, F. C.: The Establishment of Collateral Circulation Following Ligation of the Thoracic Duct, Bull. Johns Hopkins Hosp. **33**: 21-31, 1922.
12. Olechowski, L. W., and Froyd, J. H.: Chylous Ascites of Unknown Cause, U. S. Armed Forces M. J. **3**: 143, 1952.
13. Huber, F., and Silver, H. M.: A Case of Acute Chylous Ascites (Non-Fatty, Pseudochylous, Lactescent of Milky Type) in a Boy 8 Years Old, Am. J. Dis. Child. **8**: 50, 1914.
14. Button, E.: Chylous Ascites With Report of a Case Treated by Venous-Peritoneal Anastomosis, Australian & New Zealand J. Surg. **15**: 306, 1946.
15. Pratt, J. H., and Mc Cready, F. J., Multiple Polyps, Multiple Intussusceptions and Chylous Ascites: Report of an Unusual Case S. Clin. North America **29**: 1209, 1949.
16. Gribetz, D., and Kanof, A.: Chylous Ascites in Infancy, Pediatrics **7**: 632, 1951.

NEPHROTIC SYNDROME IN A NEONATAL PREMATURE INFANT

Report of a Case

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BY CLINICAL standards the nephrotic syndrome is a relatively clear-cut disease. The patient demonstrating edema, albuminuria, hypoalbuminemia, and hyperlipemia is usually accepted as fulfilling the criteria necessary for this diagnosis. However, the basic mechanism of nephrosis is not clearly understood. Two distinct concepts concerning the underlying disease process are championed by the pediatrician and the internist. Generally, the pediatrician would prefer to picture lipoid nephrosis as a disease entity occurring in children. The internist visualizes the disease as a phase or stage of chronic glomerulonephritis, beginning with an episode of acute glomerulonephritis, and in the course of renal deterioration demonstrating the nephrotic syndrome.

The case presented represents an instance in which the nephrotic syndrome was manifested in a premature infant. Clinically and by laboratory standards, this case fulfills the currently accepted diagnostic criteria of lipoid nephrosis, and the pathologic findings were compatible with the diagnosis of lipoid nephrosis. The occurrence of this disease in an infant so young would seem to strengthen the argument against the concept that the nephrotic syndrome must be preceded at some interval—at least weeks—by an episode of acute glomerulonephritis, and gives support to the concept that lipoid nephrosis is a specific disease entity.

From the Departments of Pediatrics and Pathology, City Hospital, and the School of Medicine, Western Reserve University.

CASE REPORT

Baby G., a premature Negro male, was born at Cleveland City Hospital on Jan. 29, 1952, after 8½ months' gestation and twenty-hour labor. The mother was a 36-year-old Negro woman, para vi, gravida vii. Past history revealed that the mother had chronic pelvic inflammatory disease, but no history of syphilis. She had an incomplete abortion in 1946. Her serology was negative, blood type O and Rh positive. The five living siblings, aged 17, 12, 10, 9, and 7 years, were entirely well. The pregnancy was uncomplicated except for exogenous obesity. Labor and delivery were uneventful. One and one-half hours before delivery 40 mg. of Nisentil* were given intramuscularly. No other analgesia or anesthesia was used. The infant cried and breathed spontaneously following aspiration of mucus from the nasopharynx. Birth weight was 2,110 grams. The infant was transferred to the premature nursery one and one-half hours after delivery.

Physical examination four hours after delivery revealed a normally developed, premature Negro male who had good color, a lusty cry, and was quite active. There was unusual flaring of the costal margins with inspiration, but the lungs were clear and the breath sounds were well

transmitted. The remainder of the physical examination was entirely normal.

The infant was placed in an incubator with increased oxygen. Other than menadione, 2.5 mg. I.M. b.i.d. for three days, no medications were given. On the fifth day of life the infant developed signs of respiratory distress, with sternal retraction and cyanosis. Procaine penicillin, 50,000 units intramuscularly daily, and streptomycin, 50 mg. intramuscularly every 8 hours, were started. A nebulizer was used to increase the humidity within the incubator. On the following day periorbital edema was noted and from this time on the infant was never entirely edema free.

The infant continued to suffer from respiratory distress despite oxygen, increased humidity, and antibiotics. Coughing became a prominent symptom, and large amounts of nasopharyngeal mucus necessitated frequent aspiration. Rapid respirations and episodes of cyanosis were noted repeatedly. Feedings were usually taken eagerly. On the sixteenth day of life râles were heard diffusely through the chest, and there was evidence of right upper lobe atelectasis which was confirmed by x-ray. The liver was now palpable three fingerbreadths below the costal margin, and a left inguinal hernia had developed. On the eighteenth day edema of the eyelids, hands, and feet was observed and the patient's color was dusky. Râles were audible over the right upper lobe. The abdomen was soft and both kidneys were now easily felt. By the twentieth day the abdomen was distended. Radiographs of the abdomen and chest revealed paralytic ileus and continued right upper lobe atelectasis and pneumonic infiltration in the left lung. Distention was relieved by rectal tube and enemas. The formula was changed at this time from a simple evaporated milk formula to Lonalac.

*Nisentil, a synthetic narcotic 1,3-dimethyl-4-phenyl-4-propionoxy-piperidine hydrochloride (Hoffmann-La Roche).

By the twenty-sixth day the infant had gained 1,170 grams. Four urinalyses, performed on the eighth, eleventh, seventeenth, and twenty-fifth hospital days, all revealed 3 plus albuminuria. The fourth specimen also revealed occasional white blood cells, from 0 to 3 red blood cells, and an occasional hyaline and finely granular cast per high-power field in the uncentrifuged specimen.

On the twenty-ninth day, the blood urea nitrogen was 13.7 mg. per 100 c.c., the serum cholesterol 218 mg. per 100 c.c.; the total serum proteins were 2.1 grams per 100 c.c. with albumin 0.7 gram. The following day the blood cholesterol was 312 mg. per 100 c.c., the total serum proteins 1.5 grams per 100 c.c., the total serum lipoids 1,090 mg. per 100 c.c., and the blood urea nitrogen 17 mg. per 100 c.c.

On the thirty-first hospital day ACTH was started. The infant was given 5 mg. intramuscularly three times a day for seven days, 3 mg. intramuscularly three times a day for one day, and 1 mg. intramuscularly three times on the final day of treatment. In addition 0.75 Gm. of potassium citrate was given daily throughout this course of therapy. The infant appeared to be improved, and respiratory distress disappeared. Edema was less apparent although the albuminuria continued. On the forty-fourth hospital day the blood phosphorus was 5.1 mg. per 100 c.c., alkaline phosphatase 1.9 Bodansky units; the cephalin flocculation test was negative in twenty-four hours, and 2 plus in forty-eight hours.

The gain in weight was rapid during the first three weeks of life, so that the infant weighed 3,250 grams on the twenty-fourth day. Following the course of ACTH therapy the infant's weight dropped and remained approximately 2,700 grams until the seventy-third day when he again began to gain. On the fifty-ninth day a chest x-ray was entirely normal. An x-ray skeletal survey was normal.

Intravenous pyelograms and cystograms were negative. There were 3 grams of albumin per liter of urine on a twenty-four-hour urine specimen.

On the seventieth day evidence of respiratory distress recurred. The infant gradually developed pitting edema over the entire body. On the seventy-second day the blood cholesterol was 236 mg. per 100 c.c., cholesterol esters 152 mg. per 100 c.c., total serum protein 2.1 grams per 100 c.c., with albumin 0.8 gram, and serum lipoids 1,250 mg. per 100 c.c. A second course of ACTH was initiated, 5 mg. three times a day for eight days, 5 mg. twice a day for two days, and 5 mg. for one day. At the end of this therapy, 3 plus albuminuria persisted; urine specific gravity was 1.024, and blood urea nitrogen was 9.1 mg. per 100 c.c.

On the eighty-seventh day the abdomen was markedly distended, and the infant was in extreme respiratory distress. An abdominal paracentesis was performed and 300 c.c. of slightly milky fluid with a specific gravity of 1.006 and proteins of 30 mg. per 100 c.c. was removed. A 50 c.c. whole blood transfusion was given. During the following week two more paracenteses were performed with the removal of 300 and 400 c.c. of similar fluid. The infant's condition remained poor. Evidence of consolidation of the right lower lung developed, and the infant died on the hundred and third day of life. The entire hospital course was afebrile except for high

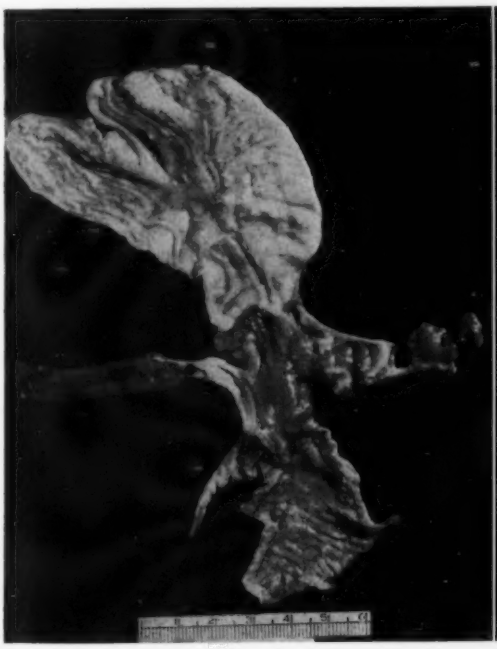

Fig. 1.

Fig. 2.

Fig. 1.—Gross picture of stomach, duodenum, and gall bladder showing calculus in cystic duct.

Fig. 2.—Gross picture of the kidneys, ureters, bladder, and abdominal aorta showing patent renal arteries. The renal veins were also patent.

temperature spikes on the eighty-ninth and one hundred and first days.

Autopsy Findings.—The body was that of a normally developed and well-nourished Negro male approximately 3 months of age. An umbilical hernia was present and measured 1 cm. in diameter. It was easily re-

Fig. 3.

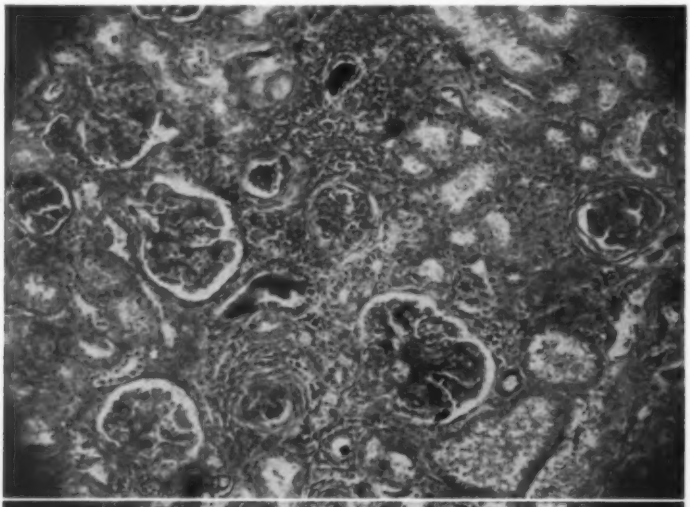

Fig. 4.

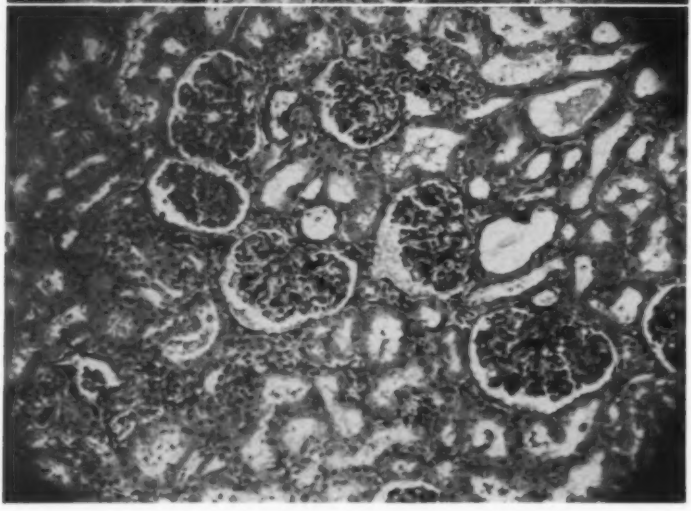

Fig. 3.—Photomicrograph of kidney cortex showing focal obliteration of glomeruli and lymphocytic infiltration in interstitial tissue. Several surrounding glomeruli show obliteration of capillary tufts and thickening of the basement membrane with PAS-positive material. (PAS stain, hematoxylin counterstain ×185, using No. 58 Wratten green filter to bring out PAS-positive material.)

Fig. 4.—Photomicrograph of kidney cortex showing epithelial and endothelial proliferation and focal thickening of the basement membrane. (PAS hematoxylin counterstain ×185, using No. 58 Wratten green filter to bring out PAS-positive material.)

duced. The abdomen was markedly distended, and 275 c.c. of opalescent fluid with a specific gravity of 1.010 was present in the peritoneal cavity. The scrotum was edematous, but the extremities showed no edema. The remainder of the gross examination was negative.

Fig. 5.

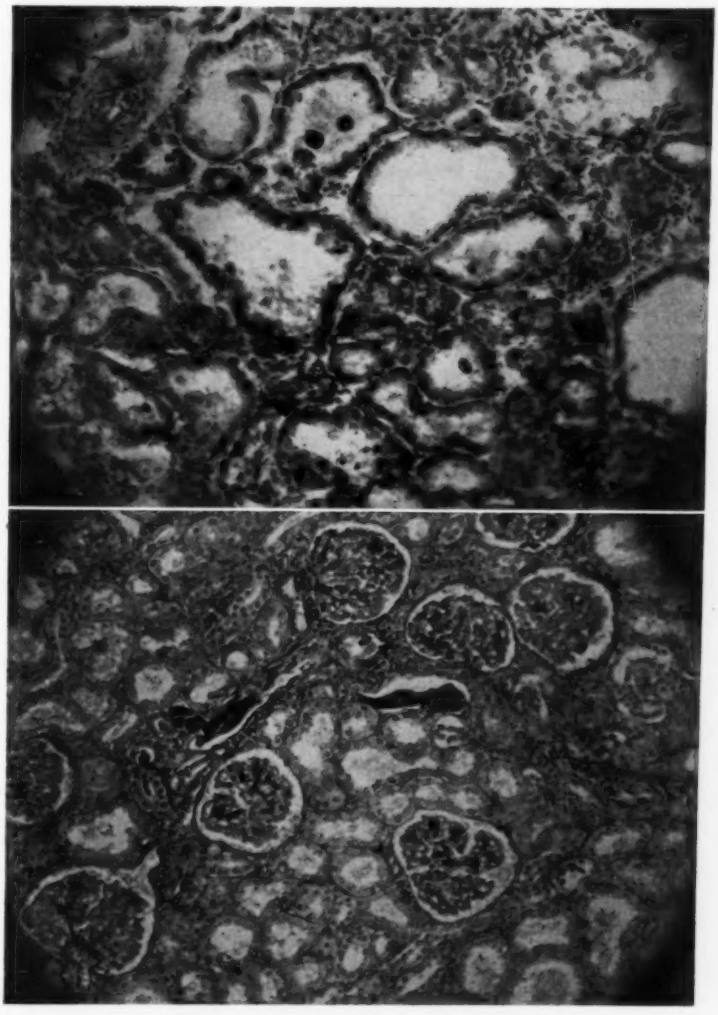

Fig. 6.

Fig. 5.—Photomicrograph of kidney medulla showing Sudan-positive particles in tubular epithelial cells and in lumina. In the upper left is a thickened arteriole showing medial hyperplasia and narrowing of the lumen. (×185. Sudan red stain with hematoxylin counterstain, using No. 58 Wratten green filter to bring out Sudan red particles.)

Fig. 6.—Photomicrograph of kidney cortex showing dilated capillary tufts, proliferation of epithelial and endothelial cells, PAS-positive casts in tubules, and precipitated protein material in tubules. (PAS stain with hematoxylin counterstain ×185, using No. 58 Wratten green filter to bring out PAS-positive material.)

The heart and great vessels were normal. The heart weighed 16.4 grams. The right lung weighed 29 grams, and the left 37 grams. There were a few small areas of atelectasis and pneumonic consolidation. Microscopic examination of the lungs showed foci of bronchopneumonia in all three lobes of the right lung. Numerous vacuolated macrophages were found in the alveoli of all lobes and in the bronchioles of the right lung. The most striking microscopic finding in the lungs, however, was the acute and chronic bronchiolitis found bilaterally. Small fibrin thrombi were also present in several small vessels bilaterally. Patchy foci of atelectases were scattered over both lungs. Many of the bronchioles and alveoli were filled with a thick proteinaceous material.

The liver weighed 183 grams, the spleen 12 grams, and the abdominal viscera were not remarkable except for the gall bladder which contained several soft, black calculi. One of these was present in the cystic duct (Fig. 1).

The right kidney weighed 35 grams, the left 35 grams. The capsular surfaces were smooth and dark red in color. The cortical layer was well preserved and the corticomedullary border was distinct. The medulla was pale. The pelves, ureters, and renal vessels were not remarkable (Fig. 2).

Miscroscopic examination revealed small and infrequent foci of chronic inflammatory cells, particularly lymphocytes in the interstitial tissues and a few obliterating glomeruli (Fig. 3). The vast majority of the glomerular tufts were dilated and contained numerous red blood cells, but only rare leukocytes. The basement membranes of glomeruli were not thickened. These were studied by the periodic acid Schiff method. The majority of the glomeruli showed some cellular proliferation, but little or no edema of the interstitial tissue. The cellular proliferation appeared predominantly in the region of the mesangium and the nuclei of the mesangial cells showed little vesiculation or swelling (Fig. 4).

The tubular lumina contained a precipitated protein material. The tubular epithelium was swollen, but there was no desquamation or necrosis. A small amount of lipoid material was present in the tubular epithelium and in macrophages within the tubular lumina (Fig. 5). The luminal "brush" border of the proximal convoluted tubules stained positively for alkaline phosphatase. This stain was performed in order to gain some idea of the functional enzyme systems of the tubular epithelium, and this was interpreted as being normal as regards alkaline phosphatase. Several of the tubules contained dense casts which stained positively with the PAS stain (Fig. 6).

Several of the medium-sized arterioles showed hyperplasia of the cells of the medial coat, resembling the hyperplastic arterioles in benign nephrosclerosis.

The final anatomical diagnoses were: (1) lipoid nephrosis, (2) bronchopneumonia, right, (3) acute bronchitis and bronchiolitis, (4) cholelithiasis and choledocholithiasis, and (5) ascites, 275 c.c.

DISCUSSION

Bell,[1] in his study of the glomerular lesions in patients exhibiting the clinical syndrome of lipoid nephrosis, has divided the group into three subgroups. They are: (a) those cases which anatomically are proliferative glomerulonephritis, (b) the cases which anatomically show proliferative and membranous lesions with a predominance of the latter, (c) the cases which anatomically show no evidence of proliferative glomerulitis.

The case described herein falls into the last mentioned subgroup. Bell further points out that in young children, the basement membrane

lesions are not present at all or only focally present, while in older children and in adults thickening is almost always pronounced. He further indicates that the lack of basement membrane thickening is not related to the duration of disease since three of his patients showing no glomerular basement membrane lesion at all were from 13 to 16 months' duration. He believes "the capacity of the membrane to thicken in response to injury is in some way related to age."

Ehrich and Forman,[2] studying eight cases of lipoid nephrosis with the aid of the Ritter and Oleson polysaccharide stain, found that in four the only lesion was focal thickening and splitting of the basement membrane in the majority of the glomerular tufts, although some tufts appeared normal. They also noted proliferation of the visceral and parietal epithelial cells in some cases.

Jones[3] acknowledges that minor degrees of glomerular scarring are present and that thickened basement membranes have been described as the primary cause of lipoid nephrosis. He finds, however, that juvenile lipoid nephrosis is characterized by an increase in a number of mesangial cells and the irregular increase in the connective tissue in the glomerular stalk.

The rather sparse, anatomical findings in the present case are not unlike those found in similar cases of lipoid nephrosis. These findings are characterized by (a) focal glomerular scarring and interstitial chronic inflammatory cells, (b) the lack of basement membrane thickening and cellular proliferation in the majority of the glomerular tufts, although a small number did show these changes to a minor degree, (c) the hyperemia of the capillaries of the glomerular tufts, (d) the presence of a small amount of lipoid material in the tubular epithelium and the presence of alkaline phosphatase in the brush border of the epithelium of the proximal convoluted tubules. These appear perfectly compatible with the histological pattern noted in other reported cases of lipoid nephrosis.

CONCLUSION

The nephrotic syndrome is rarely described in the very young infant. Lyttle and Goettich[4] mention its occurrence in an infant 3 weeks old. It is impossible to say when the nephrotic process started in this case. The edema noted on the fifth day of life cannot be positively attributed to this disease in view of the fact that the infant was premature. However, urinalysis on the eighth day, in which a 3 plus albuminuria was demonstrated, would suggest that the process had begun before this time.

The case presented fulfills the more commonly accepted criteria for the diagnosis of lipoid nephrosis. The clinical response of the patient to the initial course of ACTH suggests that the disease process was "pure" nephrosis rather than a nephrotic syndrome associated with some renal anomaly or renal vein thrombosis. The infant succumbed to bronchopneumonia without showing evidence of reduced renal function.

The laboratory and clinical evidence as well as the pathologic findings were compatible with the diagnosis of lipoid nephrosis. So far as can be determined this case represents the earliest reported appearance

of this disease. The case does not shed light on the pathogenesis of this disease, but does support the contention that lipoid nephrosis is a disease of the infant and young child, separate and distinct from the nephrotic phase of chronic glomerular nephritis.

REFERENCES

1. Bell, E. T.: A Clinical and Pathological Study of Subacute and Chronic Glomerulonephritis, Including Lipoid Nephrosis, Am. J. Path. **14**: 691, 1938.
2. Ehrich, W. E., and Forman, C. W.: quoted by Barnett, H. L., Forman, C. W., and Lauson, H. D.: The Nephrotic Syndrome in Children, in Levine, S. Z. (ed.): Advances in Pediatrics, vol. 5, Chicago, 1952, Year Book Publishers.
3. Jones, D. B.: Glomerulonephritis, Am. J. Path. **29**: 33, 1953.
4. Lyttle, J. D., and Goettich, Elvira: Nephritis and Nephrosis, in McQuarrie, I. (ed.): Brennemann's Practice of Pediatrics, Hagerstown, Md., 1950, W. F. Prior Co., Inc.

PAROXYSMAL TACHYCARDIA WITH A CEREBRAL EMBOLUS

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THERE are several reviews in the literature summarizing the reported cases of paroxysmal tachycardia. Few central nervous system complications are reported. Nades and associates,[1] in a study of forty-one cases, report one patient dying of cardiac failure and cerebral embolism due to a mural thrombi in the ventricle of the heart. Levine[2] reports an adult with several embolic phenomena ultimately resulting in gangrene of an extremity. He attributes the thrombolic sequela to low pulse pressure and minute cardiac output during the attacks. Philipsborn and Gibson[3] report an infant, aged 1 month, having an associated extensive cerebral hemorrhage causing death.

CASE REPORT

M. G., a 4-year-old white male, was brought to the Nebraska Methodist Hospital because of vomiting intermittently for two days and abdominal pain for twenty-four hours. The day of admission, the child had pain in the midepigastrium near the umbilicus. No change in bowel habits was reported.

Past history revealed frequent upper respiratory infections associated with nasal obstruction.

Physical examination revealed a lethargic child in apparent distress, especially on movement. The heart was rapid with a regular continuous rate of 280 per minute. No murmur was heard. The abdomen was tender to palpation, and the liver was felt 3 cm. below the costal margin in the midclavicular line. The left lobe extended past the midline and was tender. The tip of the spleen was palpable.

Laboratory data showed hemoglobin 12.5 grams, red blood count 4,520,000 white blood count 11,200, polymorphonuclears 63, basophils 3, lymphocytes 27, monocytes 7. Sedimentation rate of 19 (Wintrobe uncorrected). The urine was clear. An x-ray of the chest showed slight cardiac enlargement with pulmonary congestion.

An electrocardiogram after restoration of the heart rate to 112 showed changes consistant with right heart dilatation.

The diagnosis was paroxysmal tachycardia with right heart failure.

Progress.—Treatment consisted of sedation with paraldehyde, and digitalization. Within twelve hours, the heart rate dropped to 112, and the patient was sitting up in bed eating breakfast.

At 3:00 P.M. the same day, his eyes suddenly rolled back. He became restless, could not speak or respond to questions, and developed a right hemiplegia. Physical examination revealed a supple neck, blood pressure 118/70, right hemiplegia including the face, temperature 99.6° F. pulse 100, and respirations 32. No further paralysis occurred. Eight days later the aphasia disappeared and motion began to return to his right leg. Within fourteen days, he had recovered except for a slight residual paralysis in the lower right face and decreased motor power in the right

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shoulder girdle. A follow-up visit in the office ten days later showed further recovery.

X-ray examination of the skull and an electroencephalogram were negative prior to dismissal from the hospital.

DISCUSSION

Because of the few reported cases in the literature concerning cerebral complications in childhood following attacks of paroxysmal tachycardia, this case is reported. The embolus may have formed during the period of minute cardiac output and low pulse pressure. A right hemiplegia resulted. Functional recovery in this child occurred.

SUMMARY

1. A case of paroxysmal tachycardia in a 4-year-old child is presented.

2. The complication of an embolus to the middle cerebral artery produced a right hemiplegia and aphasia.

3. Functional recovery occurred.

REFERENCES

1. Nades, A. S., Daechner, E. W., Roth, A., and Blumenthal, S. L.: Paroxysmal Tachycardia in Infant and Children, Study of 41 Cases. Pediatrics **9**: 167, 1952.
2. Levine, S. A.: Clinical Heart Disease, ed. 4, Philadelphia, 1951, W. B. Saunders Co., p. 213.
3. Philipsborn, H. F., and Gibson, S.: Paroxysmal Tachycardia in Infants—Report of Two Cases Treated With Intravenous Acetylcholine Bromide, Pediatrics **1**: 205, 1948.

THE ORIGIN OF OBSTETRIC NURSERIES

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THE practice of caring for newborn infants in separate nurseries appears to have been an American contribution, but the "when and why" seems to have escaped the memory of the oldest inhabitants. On the other hand, the younger generation has never known anything but newborn nurseries. Therefore the reasons for the origin of nurseries and for the present trend back to rooming-in should be explained.

There is a possibility that the English may dispute this "honor" of inventing newborn nurseries, as Weymuller[1] quotes Dr. Claude Heaton, author of *Colonial Obstetrics,* as saying, "The first nurseries he knows about were established in London at the end of the 17th century. They were the project of a retired sea captain who gave his funds and interest to the management of a home for wayward girls and their offspring." However, these nurseries were probably foundling homes and not obstetric nurseries in the present sense.

In 1930 Douglas[2] spent nearly a year visiting practically all the European clinics and found that almost all of the older institutions used the rooming-in principle. This was particularly true in England—the exception to the rule was the new hospitals in the Scandinavian countries and Germany where nurseries were employed.

Dr. Winford Smith[3] reports that obstetric nurseries appeared in the Johns Hopkins Hospital some time after the opening of the hospital in 1889. They were in existence when he entered the school in 1899 and he thinks they were established by Dr. J. Whitridge Williams.

The New York Lying-in Hospital is the oldest lying-in hospital in this country, having been founded in 1799. The Hamilton Fish House quartered this hospital from 1894 to 1899. Douglas[2] has a photograph (Fig. 1) of a ward demonstrating that during this period there was no nursery, the cribs being suspended at the end of the bed on davits like a lifeboat. Dr. James W. Menkoe was sent abroad in 1898 by J. Pierpont Morgan to study new hospital ideas. The final plans for this hospital included newborn nurseries. The hospital was opened for patients in January, 1902.

Thus, it appears that nurseries for the care of the newborn infant became part of the American culture between 1890 and 1900. Some of the reasons for this development are revealed in the early annual reports of the trustees and visiting physicians of the Boston Lying-in Hospital.

The Boston Lying-in Hospital was founded and incorporated in 1832. The original hospital was forced to

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close due to lack of financial support, but was reopened in 1873 on McLean Street adjoining the Massachusetts General Hospital, "for women during childbirth who from misfortune or otherwise had no home." The hospital consisted of eighteen to twenty beds and cost $16,000. During the first two years, 342 women were delivered with three maternal deaths. Considerably more than half of the admissions paid no fee at all—the lowest established fee was $20.00 for confinement and the two succeeding weeks.

Fig. 1.—Ward in the old Hamilton Fish House, 1894 to 1899. (Courtesy R. Gordon Douglas, M.D., The New York Hospital.)

The original purpose of the Boston Lying-in Hospital was to care for "that class whom maternity makes outcasts." "The time has gone by when an unfortunate woman is to be branded as an outcast, without hope of redemption in society. . . . The class of patients for whom lying-in hospitals are established always have been, and may continue to be, of difficult management, except as in Europe, where the hospitals are comparatively free and under State or Municipal laws—we do not think the time has come for this in this country; but we *do think* there should be some State authority, and laws of oversight, to guard against the temptations of mothers to commit suicide, infanticide or to desert their children in anticipation of the miseries they see before them as they exist at present."

In the early few years of operation, over two-thirds of the mothers were unmarried but by 1875 two-thirds were married. The hospital's great need was for more room so that women could be received some

little time before their confinement instead of at the onset of labor. "We have almost daily application for admission from women utterly destitute of money and friends, who beg to be allowed to come and work for their board till the time of their confinement. . . . these patients excite the deepest sympathy on our part. They occur so often that new ones crowd out the recollection of the past. . . . Many applicants cannot maintain themselves by work during the last month of pregnancy, and some are obliged to go to the almshouse by sheer necessity. Very often the applicants will have some little money saved up to pay their board, relying upon a free bed in time of labor; before this comes the money is gone, paid out to some of the numerous professed private hospitals. The money being gone, the patients are often turned out of doors, either to go to the almshouse at Tewksbury or sent to our hospital. Again there is a system of promised care in these resorts, depending on the mother agreeing after confinement to go out as wet nurse, and mortgaging her services as such, to an exorbitant extent, in return. Bad as is this condition of affairs, it is preferable and is submitted to, rather than be sent to the almshouse, so repugnant is that to the sensibilities of many women whose condition and crime are mainly brought about by poverty."

While the original purpose of the Boston Lying-in was to care for "that class whom maternity makes outcasts," the need of the times caused the trustees to deviate from this purpose with the reopening of the hospital in 1873 by adding to the above group "the large and very respectable class, with means sufficient to meet comfortably all the ordinary expenses of living, to whom the interruption and expense of childbearing is a very serious matter. To these, whether they are attended gratuitously or whether they are required to make a small return—the advantages of such an institution as a lying-in hospital are an incalculable benefit."

The decision to mix the "respectable" with the "outcasts" on the wards of the hospital took a great deal of courage on the part of the trustees. While the hospital had no ladies officially connected with it, the visiting physicians who became more or less acquainted with the circumstances, anxieties, and future prospects of the patients, called upon "several charitable ladies to aid, assist and counsel those of our patients who leave our doors friendless and homeless. In no instance has this appeal been in vain and we beg leave to express our warmest thanks to the ladies connected with the 'Society for Aiding Destitute Mothers and Infants.'" After two years of this daring experiment the trustees were able to report, "We think the experience of these two years shows that, with sufficient guards, they can be thrown together without offense to the one, and with great benefit to the other."

The hospital grew rapidly and three identical attached buildings were purchased in 1876 and 1888. In 1891 these four properties were remodeled and rebuilt as shown in Fig. 2. In the rebuilt hospital there were now seventy maternity beds, six large wards, three medium-sized wards, two isolation wards, but *no nurseries*. The

infants were placed in multiple crib units and kept in the wards with their mothers (Figs. 3 and 4).

In the annual reports of the visiting physician between 1891 and 1898 the need for a "night nursery" for the babies was frequently stressed. Even in those days there were babies whose behavior at night left much to be desired and who succeeded in disturbing the rest of the entire ward. Furthermore, many of the poor mothers in nineteenth century lying-in hospitals were too weak or too ill to care for their infants, especially at night. In 1898 "There has also been received from Mrs. Francis B. Greene, as a memorial to Bertha J. Raemisch—a former nurse of the Hospital and subsequently widely known and beloved as a masseuse—the sum of $1,000.00 to be used in such manner as might be deemed most beneficial. One of the rooms in the Hospital has been assigned as a *night nursery,* and the sum of money given by Mrs. Greene has been partially used in a complete furnishing of the nursery, which is now known as the Bertha J. Raemisch Ward, and also in providing throughout the Hospital wards a separate new day crib for each baby for the use of babies during the daytime." (Figs. 5 and 6.)

Subsequent reports do not chronicle the fate of the night nursery but conversations with the older members of the staff permit a probable reconstruction of what happened. Having a separate nursery for infants soon resulted in those infants requiring special care being concentrated in this spot and the ward babies continued to stay on the mother's ward around the clock. By 1912 the visiting physicians' annual reports were again stressing the need for a new hospital wherein nurseries could be provided for the "night care" of the babies.

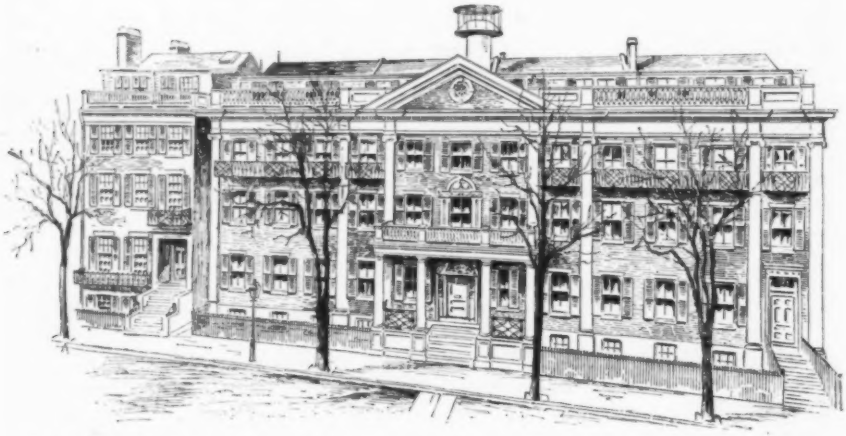

Fig. 2.—Boston Lying-in Hospital, 24 McLean Street. (From the 60th Annual Report.)

A most important force was at work convincing the trustees and physicians that the physical welfare of the infants demanded nurseries wherein they could be kept separate

Fig. 3.—A ward of convalescent patients. (From Boston Lying-in Hospital 76th Annual Report, 1908.)

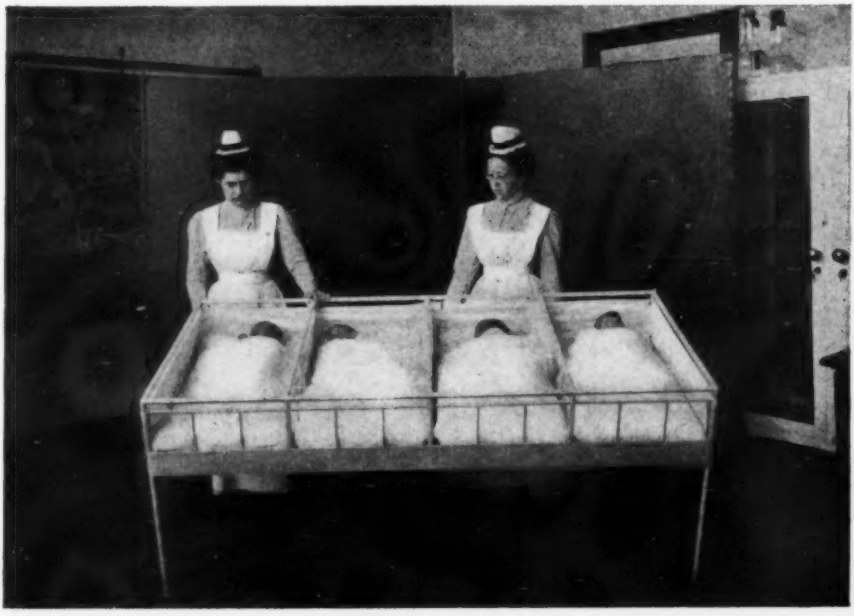

Fig. 4.—A crib of babies. (From Boston Lying-in Hospital 77th Annual Report, 1909.)

Fig. 5.—The first nursery in the Boston Lying-in Hospital. (From the 66th Annual Report, 1898.)

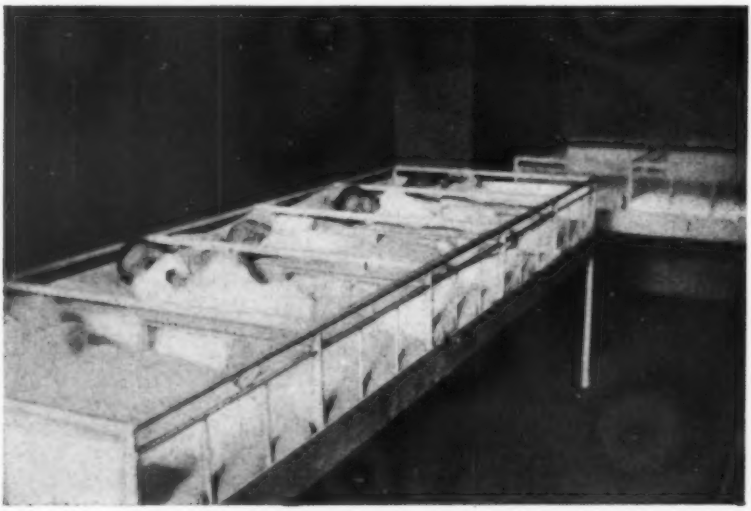

Fig. 6.—The "night" nursery. (From Boston Lying-in Hospital 66th Annual Report, 1898.)

from the mothers. In the spring of 1907 there were at one time seven babies suspected of having diphtheria, two of whom proved to have the disease. In the spring of 1908, when scarlet fever was prevalent in the community, nine mothers developed the disease during their puerperal convalescence. Seven of them were transferred to the scarlet fever wards at the Boston City Hospital with their babies, and five of the infants died. In 1911 a culture from an infant's nasal discharge was reported by the Board of Health as positive for the diphtheria bacillus. The organism was traced to a woman in the next bed with a chronic ear discharge. Cultures taken from day to day in other mothers and babies showed continued invasion of this bacillus, in spite of such isolation as the hospital afforded. The visiting physician again stressed the need for "an enlarged modern hospital in a healthful location."

With this background of practical experience we can easily understand why the designers of the new Boston Lying-in Hospital, that opened in 1922, provided ample nurseries for the care and protection of the newborn infant. The years since 1922 have witnessed widespread reduction in maternal and neonatal morbidity and mortality. Preventive medicine and the advent of chemotherapy and antibiotic therapy have reduced the hazards to which the newborn infants are exposed, and made less obvious the need for physical isolation symbolized by the nursery system.

Furthermore, with the rising percentage of American babies of the more affluent group, the carriage trade, who were delivered in hospitals (85 per cent of all American infants are now born in hospitals), the nurses, obstetricians, and possibly even the pediatricians, though there were scarcely fifty of them prior to 1900, decided that the obstetric wards and private floors would be quieter and tidier if the infants were coralled into one room, misnamed as a nursery, and only brought to the mother at regular intervals for breast feeding. Next, the evolution of infant feeding demonstrated that mixtures of cow's milk seemed to be as good as human milk, so even these four-hour visits of the infant to the mother ceased in many hospitals. That the affluence of the obstetric patients was a factor in the origin of nurseries is borne out by the fact that in Europe and Asia where the obstetric services are largely for the poor, there are no nurseries, and the babies are still placed in bassinets next to their mothers immediately after delivery.

In many institutions the cycle has completed its course. The babies have been returned to the mothers. The present trend is to have the baby with the mother as much of the day and night as she wishes but to have "night nurseries" available for use when needed. Thus the second round of the cycle is on.

Let us hope that we shall learn from history. Let us hope that a false sense of security will not cause a relaxation in the principles of good nursing technique. For the dangers of infection are real, and careful post-mortem studies reveal that infection is still a major cause of neonatal death. It is an interesting turn of the cycle that one of the reasons for the origin of nurseries was the risk of infection on the obstetric wards, and that now with modern asepsis and antisepsis, the

wards are so much safer than the newborn nursery that the risk of nursery epidemics has stimulated the return of the infants to their mothers on the wards and in private rooms. We know more about our enemy, infection; we have more efficient weapons with which to fight him, but he is still ever present and waiting for a chance to strike!

This progress also has its amusing side. A small epidemic of diarrhea in the Yokohama nursery for the newborn infants of the wives of Army personnel in 1948 caused Major General J. A. Bethea, the Chief Surgeon of the Far Eastern Command, to abandon nurseries and to establish rooming-in on the suggestion of Lt. Col. Grant Taylor, a member of the Duke pediatric staff. However, the military civil government in the meantime continued to advise the Japanese civilian hospitals to abolish rooming-in and to build newborn nurseries. Needless to say, the Japanese knowing that the Army had abandoned its nurseries, were confused for they had never used anything except rooming-in on a family scale, that is, the hospital furnished only the room and bed mat. The family brought in the bedclothes and a hibachi to cook the meals, and if the weather was very cold the mother went to bed with the child to keep him warm.

REFERENCES

1. Charles A. Weymuller, M.D., Long Island College of Medicine, Brooklyn, N. Y., personal communication.
2. R. Gordon Douglas, M.D., The New York Hospital, personal communication.
3. Dr. Winford Smith in a personal communication to Dr. Edwin L. Crosby, Director, Johns Hopkins Hospital, Baltimore, Md.

Clinical Conference

CLINICAL CONFERENCE AT ST. CHRISTOPHER'S HOSPITAL FOR CHILDREN, PHILADELPHIA, PA.*

Two Cases of Hereditary Spherocytosis Manifest in the Newborn Period

DR. WILLIAM C. ADAMS (Chief Resident Physician).—These two cases are of interest in that they involve two siblings in situations which are so far as we know unique. Dr. Hindman will present the first child.

DR. SARAH HINDMAN (Assistant Resident Physician).—Hugh Y is the third child of a mother whose first two pregnancies were uneventful and whose first two babies attracted no attention in the newborn period. The mother herself is in good health following splenectomy in 1944 for hereditary spherocytosis, at which time a cholecystectomy was done. She was 18 years old at the time. Her mother also underwent splenectomy for the same reason a year later, and the history records that the maternal great-grandfather of the patient suffered from jaundice.

Hugh was born on Sept. 26, 1951, at 6 A.M., at 38 weeks' calculated gestatory period, following an uneventful pregnancy. Labor was easy and spontaneous. The infant weighed 7 pounds 15 ounces at birth, and seemed entirely normal. Jaundice is stated to have appeared within a few hours of birth, was conspicuous by the second day of life, and was intense by the third day. Because of the severe icterus, a blood culture was done and studies made to determine whether erythroblastosis fetalis might be present. The blood culture grew no organism. The infant's hemoglobin level was 21.2 grams per cent, and red cell count 5.58 million per cubic millimeter. The white blood cell count was 12.4 thousand, and there were 5 nucleated red cells for each 100 white cells (620 per cubic millimeter). Hugh was shown to be group A Rh positive, and his mother, group O Rh positive. A Coombs test was negative with Hugh's cells. His mother was shown to have agglutinins for both Hugh's cells and other group A cells, but the anti-A did not exceed a titer of 1:16 in saline. It was felt at the time that these results made it unlikely that erythroblastosis fetalis was present. Examination of the blood smear for spherocytes was made, but a satisfactory answer was not obtained as to whether spherocytes were present.

On the fourth day of life the infant began to have spasms of opisthotonus, particularly when disturbed, and fed less well than before. On the fifth and sixth days opisthotonos continued to be conspicuous, after which it was not seen except for an isolated observation on the fourteenth day. Icterus began to fade on the seventh day, and had disappeared by the twelfth day.

By the sixth day of life the hemo-

From St. Christopher's Hospital for Children, Department of Pediatrics of Temple University School of Medicine.

*Edited by Rudolf Roddy, M.D., Chairman of the Conference.

globin level had fallen from 21.2 to 17.1 grams per cent, and by the thirteenth day to 11.2 grams per cent. A transfusion of 75 ml. of group O Rh-positive blood was given without incident at this time, and the baby sent home on the sixteenth day, with a hemoglobin level of 12.7 grams per cent.

During the next six weeks the infant became increasingly pale, and failed to make satisfactory developmental progress. His mother found him less responsive than her other children, and had concern for his vision. When he was eight weeks old his hemoglobin level was found to be 6 grams per cent and he was admitted to St. Christopher's Hospital for Children for study.

At eight weeks Hugh was a scrawny, fretful, hypertonic infant who lay in a predominantly opisthotonic posture, especially when disturbed. He did not appear to see objects in his line of vision and had no social smile. Physical examination was not otherwise remarkable. Liver and spleen were not felt.

Laboratory studies disclosed a hemoglobin level of 5.6 grams per cent, red blood cell count 2.01 million, reticulocyte count of 5.8 per cent, and bilirubin level of 0.4 mg. per cent. The peripheral blood showed many spherocytes, with some increase in fragility, and marrow was hyperplastic with respect to erythroid elements. It was the consensus at this time that the infant presented hereditary spherocytosis, with kernicterus. A splenectomy was performed after transfusion therapy. The procedure was well tolerated, and appears to have put an end to the hemolytic process.

Hugh's subsequent development has continued to be retarded. He began to appear to see at about 3 months, and smiled shortly thereafter. At one year his developmental level was estimated at somewhat less than 26 weeks, and at 2 years tests again suggest about 50 per cent retardation. He is an expressive, likeable, responsive boy at the present time (his age is 2 years), but his performance is meager, he lacks speech, and is just beginning to walk with support. His hearing is normal.

DR. ADAMS.—Dr. Baird, you have seen this boy. Would you care to comment on his neurological status?

DR. HENRY W. BAIRD, III (Assistant Attending Pediatrician, Neurology).—I think we will all agree that this is an unusual situation. I know of no other instance where kernicterus appears to have followed an episode of hemolysis or icterus due to hereditary spherocytosis in the newborn period. The description of this boy's illness in the first week is typical of kernicterus, and his present status is also entirely consistent. He is a severely involved child who has increased muscle tone, increased deep tendon reflexes, and definite athetoid movements. The left side is more involved than the right. Because of the motor involvement it is difficult to assign any precise level of intellectual function. He certainly is a responsive child, and seems well motivated. He may well prove trainable. Incidentally, a pneumoencephalogram was done which showed no evidence of a space-taking lesion, and a test for phenylpyruvic acid was negative.

MEDICAL STUDENT.—Dr. Hindman, were serum bilirubin levels done during the newborn period?

DR. HINDMAN.—No, they were not. I think it might be well to present the second child at this time so that they may be considered together from a number of these standpoints.

Bernadette Y. is Hugh's little sister, and she was born fourteen months later, on Dec. 10, 1952, at 2:16 A.M. She was a full-term baby, delivered normally after an uneventful pregnancy. Physical examination was normal at birth. At thirty to thirty-six hours she was found to be moderately jaundiced. Her spleen was not felt at this time, and her hemoglobin level was 16 grams per cent. On the third day of life the infant continued to be jaundiced, and the spleen became palpable at the costal margin. Hemoglobin level was 20.5 grams per cent early on this day, and fell to 16.7 late in the day, by which time the diagnosis of spherocytosis seemed likely on the basis of examinations of the peripheral blood.

On the fourth day the baby seemed more icteric, and the spleen was now felt at one fingerbreadth below the costal margin. A bilirubin level was found to be 26.6 mg. per cent. At this time the baby was transferred to St. Christopher's Hospital for Children for exchange transfusion.

An exchange transfusion was carried out when the baby was about 86 hours old, using group A Rh-positive blood. Five hundred sixty-five milliliters were given and 580, ml. removed by way of the umbilical vein. The procedure was well tolerated. Twelve hours later the bilirubin level was 25.2 mg. per cent, and splenectomy was carried out shortly thereafter. Five hours after this procedure the serum bilirubin level was 18.2 mg. per cent. The jaundice faded very rapidly. Two days after operation the bilirubin level was 5.7 mg. per cent, and the baby was nearly free of icterus. There were no signs of kernicterus during the neonatal period, and Bernadette's development over the past year has been entirely normal.

DR. ADAMS.—Dr. Smith, didn't you have the opportunity of seeing both these children in the newborn period?

DR. NATHAN J. SMITH (Assistant Attending Pediatrician, Hematology).—Yes, and I might say that these cases emphasize the observation that hereditary spherocytosis may give symptoms in the newborn period, as others have experienced as well as ourselves. It suggests that it may be important to keep the infants of persons known to have hereditary spherocytosis under close observation during the first few days of life.

Spherocytes may, of course, be found in other hemolytic processes as well as in hereditary spherocytosis. Sepsis and hemolytic disease due to A or B incompatibility should particularly be considered, and are more likely than hereditary spherocytosis to be responsible for difficulties in the neonatal period. Curiously, Rh immunization does not so characteristically give spherocytes. There is no doubt that both the children presented have hereditary spherocytosis, since they continue to show characteristic changes, but the possibility exists that the neonatal episodes were due to something else. Can Dr. Vaughan tell

us how, or if, isoimmunization has been excluded.

DR. VICTOR C. VAUGHAN, III (Associate Attending Pediatrician).—I think we could be a little happier in this regard than we are. Both babies were group A and their mother is group O, so that the possibility of difficulty due to maternal anti-A certainly exists. Both babies had negative Coombs tests, but this test is more often negative than not in A or B incompatibility, when done by the usual technique.

The highest recorded titer of maternal anti-A is less than 1:16 in saline. The low titer in saline is somewhat reassuring, and even a high titer would carry only questionable diagnostic significance, since it is probable that antibody which is active in saline is not especially pathogenic to the infant and crosses the placenta only to a limited extent. In fact, anti-Rh antibodies active in saline do not cross the placenta at all, which means that illness due to Rh immunization is due to those antibodies which are active only in other media.

Present evidence indicates that a somewhat similar situation may exist with regard to the A-B-O system. Witebsky first showed that A and B antibodies not active in saline exist. He found that in the great majority of cases of probable A or B isoimmunization, after addition of A or B substance (the soluble specific polysaccharide) to maternal serum, the activity of the anti-A or anti-B in saline solution may disappear, but that the "neutralized" maternal serum still contains antibodies active in high titer against A or B cells suspended in adult serum or in certain other media. So far as Hugh and Bernadette are concerned, we can only say that we have looked as carefully as we can for this anti-A which resists neutralization, but their mother does not have any. The evidence is good, therefore, that isoimmunization is not present.

It is worth noting that group A blood was used in the exchange transfusion. I am suspicious that if isoimmunization were actually present, the apparent cessation of the hemolytic process would not have been nearly so striking as was observed with the use of group A blood. If we had it to do over again, we would have given much more serious consideration to the possibility of using group O blood, with A substance added, since whenever isoimmunization is suspected or proved, safe blood for the baby will and must be compatible with the mother's serum by the indirect Coombs technique. If this necessitates use of group O blood for an A or B baby, A or B substance should be added. At the time, however, I was so dazzled by the spherocytes and negative Coombs test that I do not think we even inquired whether the mother was group A or group O, and we did not as rigorously exclude isoimmunization before transfusion as we feel we may have done after.

MEDICAL STUDENT.—If it appeared that the hemolytic process was controlled by exchange transfusion, why was splenectomy done?

DR. HINDMAN.—Both children were patients of Dr. Cucinotta. Perhaps he will be kind enough to tell us why Bernadette was handled as she was.

DR. DOMENICO CUCINOTTA (Assistant Attending Pediatrician).—Well, with

Hugh very probably having kernicterus, and with the little girl so very jaundiced, we hoped to lower the serum bilirubin, and to remove the cells being destroyed, and, in addition, to remove the organ where they were being destroyed so that any more cells coming into the circulation from the hyperplastic marrow would have the best chance of survival. Looking back, I think we may have waited longer than we would care to in another baby with the same problem.

DR. ADAMS.—Dr. Cresson, you performed the splenectomy on both these babies?

DR. SAMUEL L. CRESSON (Associate Attending Pediatric Surgeon).—Yes. This is one disease of children where it seems splenectomy should be done as soon as the diagnosis is made. We believe that the second infant is the youngest to have a splenectomy for this indication. Both babies tolerated the procedure well, as very young babies are likely to do. A skilled anesthesiologist, of course, contributes a great deal to the safety with which such major procedures can be done. Both infants showed the expected rise in platelet count after splenectomy. I believe only one was treated with heparin, however.

DR. HINDMAN.—Yes, Bernadette received heparin on the ninth and tenth days after operation, when her platelet count was hovering around 1.35 million. Hugh's highest count was 600,000 on the ninth day. It was our intention to use heparin if the count went above one million.

MEDICAL STUDENT.—Did the spleens show the typical changes of hereditary spherocytosis?

DR. JAMES B. AREY (Pathologist).—There is some doubt in my mind as to whether there are any constant changes in the spleen which are typical of hereditary spherocytosis. The changes that have been described may in part be due simply to the fact that the spleen has been removed surgically rather than at post mortem. Hugh's spleen weighed only 16 grams, which is at the upper limit of normal size for two months. Bernadette's was 18 grams, which is about two to three times normal size. Both showed hemosiderosis, consistent with a hemolytic process, but this was very much more severe in the spleen removed at the later time in the course of the disease. The younger spleen, by contrast, showed a good deal of erythrophagocytosis and erythropoiesis.

DR. WALDO E. NELSON (Professor of Pediatrics).—It seems to me that we can summarize this discussion by saying that these two children in the same family have had a hemolytic episode in the neonatal period due to hereditary spherocytosis. The first child seems to have developed kernicterus, and the second was treated by exchange transfusion and splenectomy and did not develop kernicterus. I do not suppose you mean to imply that the reason the second baby did not develop kernicterus is necessarily because of the exchange transfusion and splenectomy.

DR. VAUGHAN.—No. This may be so, but the little girl may have been out of danger already at birth. We know that girls are less likely to get kernicterus than boys, and that more mature infants are less likely than immature infants. Both of these fac-

tors weighed in favor of the second child. We *can* say that the treatment seemed reasonable and the result was satisfactory, and that we may anticipate that other situations will arise in newborn infants where kernicterus seems a possible result of a process leading to severe jaundice. In such cases it may seem as reasonable as here to attempt to control a hemolytic process and abate jaundice through exchange transfusion as well as through any more specific measures available.

ADDENDUM.—Since this report was prepared, we have had occasion to carry out splenectomy in a newborn infant of 54 hours of age with progressive jaundice due to hereditary spherocytosis. Exchange transfusion was not done since the preoperative bilirubin level was only 10 mg. per cent. The hemolytic process seemed promptly controlled by splenectomy. The bilirubin level 9 hours after splenectomy was 5.9 mg. per cent.

Presentation of a Patient With Thrombotic Thrombocytopenic Purpura

DR. SALVATOR ROSELLO (Resident in Pediatric Hematology).—This 20-month-old white female infant was admitted to St. Christopher's Hospital for Children with a presumptive clinical diagnosis of acute leukemia. She had been in normal, good health until nine days prior to admission, at which time she suddenly became ill with moderate fever and experienced one episode of vomiting of partially digested food. A physician was consulted at that time who found a fever of 102° F. and a few petechiae on the buccal mucosa. He prescribed an unknown antipyretic drug, and daily injections of penicillin were started. Forty-eight hours after the onset of the illness a discrete, macular, erythematous rash appeared on the extremities and a diagnosis of rubeola was made. Following the appearance of the rash the fever became more pronounced, with temperature elevations as high as 106° F. Additional penicillin was given and several doses of a sulfonamide were prescribed. On the fifth day of her illness she was admitted to another hospital where the rash was noted to have become very hemorrhagic, with petechiae and purpura widespread over the extremities, face, and trunk. There was severe ataxia; she could neither stand nor sit without support. At that time the hemoglobin was 8 grams per cent, the leukocyte count was 9,500 per cubic millimeter. The infant appeared acutely ill. She was treated with parenteral fluids and transfusions of whole blood; penicillin and Terramycin were given for four days. Despite this therapy her clinical condition became progressively worse. On the ninth day of her illness the leukocyte count was 124,000 per cubic millimeter and the platelet count 88,000 per cubic millimeter. The diagnosis of leukemia was highly suspected, and the patient was referred to this institution nine days after onset of her illness.

At the time of admission she was acutely ill, with a temperature of 105.8° F. (R) and a pulse of 150 beats per minute. There was an extensive hemorrhagic rash covering most of the body. The face was obviously edematous and in many of the areas, where the purpura was extensive, there was a notable degree of subcutaneous

edema. The patient was unable to respond to spoken commands and responded only slightly to painful stimuli. The edge of the liver was palpable 3 cm. below the costal margin.

Review of the infant's past history failed to reveal any significant illnesses prior to the onset of the current difficulty. The family history was negative. There were no other siblings. The allergic history was completely negative, both with respect to the patient and the members of her immediate family. Upon admission to the hospital, the following laboratory studies were obtained: hemoglobin, 8.1 grams per cent; red blood count, 3.72 per cubic millimeter; white blood count, 33,100 per cubic millimeter; platelets, 80,000 per cubic millimeter; reticulocytes, 6.0 per cent. Differential leukocyte count: band forms neutrophils, 30 per cent; polymorphonuclear neutrophils, 57 per cent; eosinophils, 0 per cent; lymphocytes, 9 per cent; monocytes, 4 per cent. Total protein, 3.75 grams per cent; albumin, 2.24 grams per cent; globulin, 1.51 grams per cent; blood pH, 7.32; CO_2 content, 20.8 meq. per liter; chlorides, 103 meq. per liter; total base, 143 meq. per liter; sodium, 136 meq. per liter; potassium, 3.66 meq. per liter; bilirubin total, 3.8 mg. per cent; (direct, 1.5 mg. per cent, indirect 2.3 mg. per cent). Urinalysis was negative. Tourniquet test was positive.

The patient's course in the hospital was characterized by progressing lethargy and eventual coma, extension of the severe hemorrhagic rash, and persistence of the generalized edema.

Blood counts done daily revealed little change from that recorded on admission. The total leukocyte count decreased somewhat and the anemia became more pronounced. Bone marrow aspiration biopsy taken on the first hospital day revealed normal, active erythropoiesis, active granulopoiesis, and a normal number of megakaryocytes. Many reticulum cells were seen, in which there were extensive erythrophagocytosis and leukophagocytosis.

Several blood cultures were negative as was culture of the urine. Agglutination studies for typhoid, paratyphoid, Brucella, and Proteus OX_{19} were negative. An "L.E." preparation was negative. The direct and indirect Coombs tests were negative. Roentgen films of the chest were normal on admission and on the fourth hospital day. An electrocardiogram showed only low voltage in all leads and tachycardia. Because of the inability of the patient to take nourishment and liquids orally she was given parenteral fluids throughout her hospital course.

During the first forty-eight hours in the hospital her condition changed very little. Terramycin was given intravenously, and cortisone 25.0 mg. was given intramuscularly every six hours starting on the second hospital day. On the third hospital day a biopsy of the skin was performed. The patient had several convulsions and became comatose on the third day in the hospital. The anemia became moderately severe, and two blood transfusions were given on the fourth day. The patient expired on the fifth hospital day.

Dr. Nathan J. Smith (Assistant Attending Pediatrician, Hematology).—This girl was admitted to this hos-

pital with severe manifestations of an acute hemorrhagic disorder. The bleeding seemed to be from multiple small areas over most of the body, resulting from some defect in the hemostatic mechanism which normally prevents the loss of blood from small vessels. As this hemostatic mechanism is dependent upon the presence of (1) an adequate number of normally functioning platelets, and (2) intact blood vessels, any dysfunction of this mechanism with its resultant petechiae and purpura must be due to a defect in one of these components. Vascular defects, in contrast to hemorrhagic manifestations secondary to defective platelets, are often associated with loss of plasma into the tissues and resultant local or generalized edema. The edematous character of many of the lesions in this patient led us to strongly suspect the clinical diagnosis of some type of vascular purpura. The very critical condition of the patient at the time of admission, however, could not be entirely explained on the basis of any of the more common types of vascular purpura.

The initial laboratory studies aided in directing us toward the correct diagnosis. The low level of hemoglobin associated with an elevated reticulocyte count, in the absence of any signs of significant blood loss, indicated that this hemorrhagic disorder was further complicated by the presence of a hemolytic anemia; the moderate elevation of the indirect bilirubin supported such a conclusion. The very low platelet count was surprising in a patient who was believed to be suffering from a hemorrhagic disturbance of vascular damage.

Examination of the bone marrow revealed two findings of interest, i.e., megakaryocytes were present in normal numbers and there was a striking degree of erythrophagocytosis and leukophagocytosis, indicating some degree of sensitization to erythrocytes and leukocytes.

Reviewing the problem in light of these studies a triad of symptoms could be recognized that have been encountered with increasing frequency in adult patients, but to date have rarely been described in children. These findings are: thrombocytopenia, hemolytic anemia, and bizarre central nervous system findings. This triad has been thought to be characteristic of thrombotic thrombocytopenic purpura. With this diagnosis in mind, paraffin sections of the bone marrow aspirate were examined in the hope of finding small blood vessels which might be involved in the vascular lesions that characterize this disease. The sections did not contain adequate numbers of small vessels for examination, and therefore a biopsy of the skin was performed. The cutaneous and subcutaneous tissue contained a few vessels which were surrounded by loose edematous tissue containing a mild to moderate infiltrate of lymphocytes. Other vessels located in the subcutaneous fat contained acidophilic hyaline thrombi within their lumens. The walls of the affected vessels were loose, necrotic, and occasionally infiltrates of cells were present within the necrotic segments of their walls.

The findings in the specimen of skin established the diagnosis of thrombotic thrombocytopenic purpura. The disease to date has been universally fatal, and the course in this girl was that of a rapidly progressing fatal disease.

The process did not appear to be significantly influenced by the administration of therapeutic doses of cortisone for four days prior to death.

DR. JAMES B. AREY (Pathologist).—Post-mortem examination confirmed the clinical diagnosis of thrombotic thrombocytopenic purpura. There were generalized edema and purpura, more severe over the extremities; occasional small foci of necrosis were present in the skin of the extremities. The peritoneal cavity contained a large amount of clear straw-colored fluid; the entire bowel and its mesentery were edematous, with scattered petechiae in the former. The heart was slightly enlarged, as were the spleen, liver, and kidneys; the myocardium was flabby. No significant macroscopic alterations were noted in the central nervous system.

Histologic examination revealed widespread involvement of small vessels at many sites in the body. The involved vessels, which included small arteries, arterioles, capillaries, venules, and small veins, revealed necrosis of their walls and small mural thrombi. A perivascular infiltrate of lymphocytes, plasma cells, and large mononuclear cells was present about some of the involved vessels. Scattered thrombi were present in the absence of demonstrable necrosis of the vascular wall, especially in the pulmonary capillaries, and a few re-endothelized thrombi were present. Vascular changes in the central nervous system were minimal.

DR. SMITH.—Thrombotic thrombocytopenic purpura is a rare disease in pediatric practice. We are familiar with only a few other reports in children. The disease has been recognized in a 9-year-old boy, and Singer has reported the occurrence of this disease in an 11-year-old girl. One might well suspect that many examples of this disease go unrecognized or for various reasons are not reported.

The etiological factors responsible for the disturbance and the pathogenesis of the disease are not known. Several detailed studies of the histopathologic lesions of the disease have been made in which the primary lesions appeared to be located in small blood vessels in widespread areas throughout the body. "Hyalinoid" degeneration of the wall and of subendothelial areas in the affected vessels are often found, with vascular occlusion resulting from the accumulation of this material and possibly from deposition of a homogenous amorphous material in the lumen of the vessel over these areas of vascular damage. Early workers felt that this material was agglutinated platelets. Although commonly employed histochemical techniques have failed to reveal any differences between this material and intact blood platelets, many observers are unwilling to accept the fact that loss of excessive platelets into such "thrombi" explains the thrombocytopenia that characterizes this disease.

The widespread nature of the vascular lesions throughout the body, the hemolytic anemia, and possibly the thrombocytopenia have led most observers to feel that thrombotic thrombocytopenic purpura is a manifestation of some hypersensitivity state. A large majority of the patients have suffered from mild infections a few days to weeks prior to the onset of the disease, which have been treated

with a wide variety of antibiotics. This might be an important etiological factor in initiating the disease in susceptible individuals. Attempts to find specific laboratory support for the presence of an autoimmunologic disturbance with such techniques as the Coombs test, L. E. test, and complement titers have been consistently unsuccessful. The finding of extensive erythrophagocytosis and leukophagocytosis in the patient described here is of interest in this respect, and has been observed in other patients with this disease.

The diagnosis of thrombotic thrombocytopenic purpura depends upon maintaining a high degree of clinical suspicion in patients who present themselves with a hemorrhagic disorder manifested by petechiae and purpura. The clinical diagnosis is strengthened by finding thrombocytopenia and hemolytic anemia in association with evidences of widespread occlusion of small vessels, especially in the central nervous system; the lack of correlation of clinical and pathologic findings in the central nervous system of this patient are not entirely explained; perhaps many of the neurological findings were the result of cerebral edema, which may be difficult to recognize at post-mortem examination. Laboratory confirmation of this diagnosis may be difficult. In biopsy specimens of the skin, lymph nodes, bone marrow, and muscles, affected vessels have been found which have permitted confirmation of the diagnosis prior to death.

Treatment of the disease is completely unsatisfactory. Meachem and associates have reported an instance of the disease in which the spleen, which was removed three years prior to death, revealed typical vascular lesions of thrombotic thrombocytopenic purpura; it is impossible to say whether or not removal of the spleen favorably altered the course of the disease. Splenectomy has been performed on six other patients who were acutely ill with the disease and no beneficial effects were observed. ACTH and cortisone might be thought to be effective, but to date trials by several observers have yielded uniformly discouraging results.

It would appear from present fragmentary knowledge that thrombotic thrombocytopenic purpura is the result of a generalized hypersensitivity state of a most serious nature. It is not difficult to speculate as to the etiological significance of the widespread use of antibiotics for the treatment of mild infections that so commonly precede the onset of this and other hypersensitivity disturbances.

The incidence of thrombotic thrombocytopenic purpura in pediatric patients may well be followed with interest in future years, as the use and reuse of antibiotic agents becomes even more widespread in the treatment of mild infections in children.

REFERENCES

Barondess, J. H.: Thrombotic Thrombocytopenic Purpura, Am. J. Med. 13: 294, 1952.

Cooper, T., Stickney, J. M., Pease, G. L., and Bennett, W. A.: Thrombotic Thrombocytopenic Purpura, Am. J. Med. 13: 374, 1952.

Meachem, G. C., Orbison, J. L., Heinle, R. W., Steele, H. S., and Schaeffer, J. A.: Thrombotic Thrombocytopenic Purpura: A Disseminated Disease of Arterioles, Blood 6: 706, 1951.

Moschocowitz, E.: An Acute Febrile Pleiochromic Anemia With Hyalin Thromboses of Terminal Arterioles and Capillaries, Arch. Int. Med. 36: 89, 1925.

Congenital Aganglionic Megacolon in a Newborn Infant

DR. WILLIAM C. ADAMS (Chief Resident in Pediatrics).—We will now present a newborn infant with congenital aganglionic megacolon. Dr. Baker, will you present the case.

DR. BENJAMIN BAKER (Resident in Pediatric Surgery).—J. R., a 5-week-old white male infant, was admitted to St. Christopher's Hospital for Children on May 8, 1952, because of abdominal distention and severe constipation. He was born at full term after an uncomplicated pregnancy and delivery; his weight at birth was 7 pounds 15¾ ounces. During his first five days of life no spontaneous bowel movements occurred, but physical examination and roentgen films of the abdomen revealed no signs of intestinal obstruction. Repeated enemas were necessary; these produced foul-smelling fecal material. The original formula of SMA was changed to Mull-soy because of the possibility that the symptoms might be the result of allergy to cow's milk. No improvement occurred, however, so skimmed milk with Dextri-Maltose was substituted. This was well tolerated, and fat was gradually added. The stools, however, continued to be foul smelling and infrequent, abdominal distention gradually increased, foul flatus was passed, appetite decreased, and weight remained stationary. Vomiting occurred only once, at the age of 7 days.

Physical findings on admission revealed a pale, pasty-appearing infant weighing 6 pounds 15¾ ounces; he was very fretful when disturbed. His skin was dry and loose, and there was a noticeable lack of subcutaneous tissue. The eyeballs were sunken, the fontanels open and flat. The eyes, ears, nose, and throat were normal except for mucosal pallor. The heart and lungs were normal. The abdomen was tightly distended, and the skin over it was slightly purplish. Peristalsis was active and normal. Rectal examination revealed good sphincter tone; the rectal vault was empty.

TABLE I.

DATE	HGB.	WBC	RBC MILLIONS	HCT	CO_2 MEQ.	CL. MEQ.	PROT. GM. %	TOTAL BASE MEQ.	NA MEQ.	K MEQ.	pH
5- 8-52	9.5	21,300			14						
5- 9-52					18.5	108	5.83	147	133	3.9	7.27
5-12-52	9.2		2.9								
5-14-52	10.8		3.4								
5-15-52							5.00				
5-20-52					18.9	114	5.83	154	143	3.5	7.36
5-21-52	13.6	11,900	4.26	40							
5-23-52	14.6		4.01	40	18.1	108.5	5.15		148	4.45	7.30
5-27-52	12.5			39	19.5	111	5.49	160	148	6.10	7.46
6- 5-52	9.5	11,250	3.89								
6-12-52	14.0		4.9								
6-14-52					13.4	112	4.46	152	142	4.1	7.32

The laboratory findings during the infant's period of hospitalization are summarized in Table I.

Therapy at admission was designed to correct dehydration and acidosis. During the first twenty-four hours he received intravenous infusions of blood, 5 per cent glucose in water, M/6 lactate, and subcutaneous 2½

per cent glucose in N/2 saline. During this time he had five small pasty yellow stools. Oral feedings of glucose water with added KCl and then Nutramigen were well tolerated, and during the next week his nutritional status improved. During this time, however, there were only one or two small, solid, often foul-smelling stools passed daily, and his abdominal distention persisted.

On the eighth, ninth, and tenth days he had eight to ten small watery stools daily. The stool digested the gelatin on a roentgen film; culture of the stool yielded *B. coli* and *Pseudomonas aeroginosa*. On the eleventh day surgical consultation was requested.

Dr. Samuel L. Creeson (Associate Attending Pediatric Surgeon).—This infant's history and physical findings were suggestive of congenital aganglionic megacolon. Accordingly, a barium enema was requested.

Dr. Baker.—Dr. Keefer, will you describe your findings?

Dr. George P. Keefer (Attending Roentgenologist).—Roentgen films following barium enema, using Neuhauser technique, revealed a persistent area of narrowing in the rectosigmoid and in the sigmoid colon; proximal to this the bowel was somewhat dilated. A finding of interest was the irregularity, fraying, and loss of sharpness of the margin of the bowel throughout the entire colon, suggesting that ulcerative changes might be present.

Dr. Baker.—Because of the clinical and roentgenologic findings, laparotomy was performed on the fourteenth day. Dr. Cresson, would you describe the operative findings?

Dr. Creeson.—Exploration revealed severe dilatation of the entire colon from the peritoneal reflection of the rectosigmoid to the cecum. At the peritoneal reflection the bowel appeared to be definitely narrowed. Above this area the bowel was approximately two inches in diameter, whereas the narrowed was only ¾ inch in diameter. The narrowed area was marked with two black silk serosal sutures for later definitive surgery, and a colostomy was performed, utilizing a loop of the left half of the transverse colon; this colostomy was opened two days later. The wedge of tissue removed at the time that the colostomy was opened was examined histologically.

Dr. James B. Arey (Pathologist).—The sections of this tissue revealed the usual inflammatory infiltrate present at the site of a recent colostomy. Ganglion cells were present both in the muscularis and submucosa.

Dr. Baker.—Subsequently the infant had three to ten soft solid bowel movements daily through the colostomy. He ate well and his weight, which had dropped to 6 pounds 1½ ounces on the nineteenth day, gradually increased to 7 pounds 2½ ounces at the time of discharge. The postoperative course was uneventful except for the occurrence of an acute pharyngitis on the thirty-sixth day; this responded satisfactorily to penicillin, and streptomycin. He was discharged on the forty-first day, to be followed at home until his nutrition and growth were such that an abdominoperineal resection of his aganglionic segment could be performed under optimal conditions.

DR. WILLIAM C. ADAMS (Chief Resident in Pediatries).—Dr. Cresson, would you care to discuss this case?

DR. CRESSON. — Congenital aganglionic megacolon in early infancy is more common than one is inclined to believe. This infant's history is quite typical of that of a newborn infant with an area of spasm in the distal part of the large bowel. During the first few days of life these infants do not pass a normal meconium stool. Constipation in some infants may be complete and yet digital examination reveals an empty rectum. Other infants, however, may pass small amounts of meconium which may be normal in character or may be somewhat dry and sticky. Constipation is accompanied by abdominal distention, and rectal examination may be followed by the passage of meconium and abundant flatus.

Distention usually appears early, as in intestinal atresia or meconium ileus. The skin over the abdomen is tense and bluish purple, with dilated superficial veins. Peristaltic waves may be visible in the dilated loops of bowel, and bile-stained vomiting usually occurs. The diagnosis often entertained is that of intestinal obstruction, peritonitis, or cystic fibrosis of the pancreas. Atresia of the bowel can be excluded if an accurate history concerning the passage of meconium is obtained; meconium in the rectum, even in small amounts, strongly indicates a patent bowel. Farber test of the meconium may be helpful if carefully performed. Roentgenograms should always be taken. Dr. Keefer, would you discuss the role played by roentgenograms in the diagnosis of this condition in these small infants?

DR. KEEFER.—When intestinal obstruction is suspected in infants, roentgenograms should always be performed both in the supine and upright positions. The films taken in the supine position will reveal the presence or absence of distention of the large or small bowel, and will aid in the localization of the site of obstruction. In congenital aganglionic megacolon, the large bowel is usually distended, and films taken in the upright position often reveal levels of fluid. Films taken in a lateral position aid in localizing the distended loops of bowel.

A small barium enema with films taken in the oblique and lateral positions will not only demonstrate the location of the apparent obstruction but will also reveal the transition between the narrow segment and the dilated bowel. However, the fact should be emphasized that the roentgenologic findings in the early newborn period are often much less apparent than later in life, and early in the course of the disease distention of the colon may be minimal or absent.

DR. ADAMS.—Dr. Cresson, do you have anything to add?

DR. CRESSON.—Yes. Neither the findings of the roentgenologic examination nor the gross operative findings can be accepted as infallible evidence of the site of transition between normal and aganglionic bowel; this can be established only by biopsy of the wall of the bowel and histologic examination. Dr. Orver Swenson has demonstrated that ganglion cells may be absent for a short distance above the area of constriction noted grossly. Moreover, as mentioned previously by Dr. Keefer, in young infants the diagnosis

of congenital aganglionic megacolon may be difficult, since dilation of the colon is minimal and an abrupt change in its caliber may not be present.

DR. ADAMS.—Dr. Arey, would you care to discuss the pathologic lesions in this patient and in similar ones?

DR. AREY.—Of course, an unequivocal diagnosis has not yet been established, since there has been no opportunity to confirm the clinical diagnosis by histologic examination of the narrowed distal segment of bowel.* However, the clinical and roentgenologic findings are certainly those commonly associated with this condition. One manifestation that has been particularly troublesome in these infants has been diarrhea, occasionally having its onset following an enema. This diarrhea may be associated with ulceration of the colon, such as has been demonstrated in some of these infants at post-mortem examination.

DR. ADAMS.—Dr. Cresson, what postoperative treatment is necessary for these infants?

DR. CRESSON.—Many surgeons hesitate to perform a colostomy in a newborn infant because of the disturbances in electrolytes which may occur. This may certainly be a very difficult problem, and is one which necessitates a very carefully planned postoperative course of therapy. Studies of the levels of the various electrolytes should be performed as indicated and necessary fluids and electrolytes substituted. Great care must be taken not to overhydrate the patient and to replace necessary electrolytes. Following such a regimen, the colostomy drainage becomes relatively normal in amount and consistency in four to six days.

With respect to the site of colostomy, this should be performed in the normal bowel just proximal to the spastic or narrowed area; in infants, demonstration of the presence of ganglion cells at the site of the colostomy, by frozen section, would appear to be a valuable adjunct to visual interpretation of the site of the spastic segment. In the present instance a transverse colostomy was performed since this left a relatively long segment of bowel distal to the colostomy; this was subsequently anastomosed to the anus in the definitive "pull-through" procedure. Colostomy appears to be the treatment of choice in small infants whose general condition is such that the more definitive procedure cannot be tolerated; when the infant weighs 15 to 25 pounds, a definitive Swenson pull-through procedure can and should be done.

DR. VICTOR C. VAUGHAN, III (Associate Attending Pediatrician).—How is the diagnosis of cystic fibrosis of the pancreas excluded in these infants?

DR. CRESSON.—The stools are first examined for trypsin by the technique employing digestion of gelatin on a roentgen film. If tryptic activity is not demonstrated by this test, duodenal intubation is performed and tryptic activity is determined in serial dilutions.

DR. GEORGE P. PILLING, IV (Assistant Attending Pediatric Surgeon).—Dr. Potts recently reported a series of infants with aganglionic megacolon in

*Histologic examination of the resected segment of bowel (October, 1953) revealed absence of ganglion cells in the rectosigmoid; they were present at the proximal line of resection of the specimen.

whom serious difficulty with electrolyte balance occurred following colostomy; hospitalization of two to five months was necessary in some instances. It would seem that two factors may play a part in such difficulties, one being the amount and type of parenteral therapy given daily, and the other being the site at which the colostomy is performed. The colostomies in all of our patients have been to the left of the mid-transverse colon or in the descending colon.

DR. ROBERT H. HIGH (Assistant Attending Pediatrician).—How soon can these infants be discharged from the hospital, and what do you tell the parents about care at home?

DR. CRESSON.—The infant is discharged as soon as he is gaining weight, his wound is well healed, and his electrolyte balance is re-established. Mothers are usually frightened at first by the presence of the colostomy, but after a week or two they have no complaints or fears. They are shown how to irrigate the colostomy, and are instructed to do so daily; the importance of a rectal irrigation weekly is also emphasized. Otherwise the infant is to be treated as normal. The mother is instructed to watch closely for intestinal upsets such as diarrhea. Since these infants may rapidly become dehydrated, the mother is instructed to call her pediatrician immediately if diarrhea should occur.

This infant has had several gastrointestinal upsets since discharge, and on two occasions local hospitalization was necessary because of diarrhea. He has gained weight and a definitive pull-through procedure and closure of his colostomy were performed in October, 1953. He is doing very well and now weighs 23 pounds.

Comments on Current Literature

ANTIVIRAL SUBSTANCES

IN THE constant search for agents possibly effective against viruses, several groups of research investigators have turned to a study of molds as a potential source of substances which might in some way exert an antiviral effect. The results of some of these investigations, which have been reported recently, are of interest to the clinician. *Penicillium funiculosum,* a mold discovered originally in Guam, has been under cultural study for the past six years, and in broth culture has been shown to produce antiviral substances (Shope, 1953[1]). The behavior of this mold on culture proved to be inconstant. During the first two years of laboratory cultivation a substance occurred regularly in cultural fluids which could be used effectively in treating mice experimentally infected with the virus of swine influenza. The toxicity of this substance for mice was minimal so that it was well tolerated therapeutically.

Eventually this property of the cultivated *funiculosum* was lost, so that for the past four years of the investigation, the mold cultures could not be manipulated so as to regain the therapeutic effect against swine influenza virus. However, another substance, apparently distinct from the first, began to appear in the mold cultures. This latter substance, which was designated Helenine, was shown to influence favorably the course of infection in mice when inoculated experimentally with the virus of Columbia SK encephalomyelitis and with Semliki Forest virus.

This substance, Helenine, occurring as a by-product, as it were, during the growth of *Penicillium funiculosum* has been studied extensively. Considered at first to be a true by-product free in the culture medium, it was soon discovered to be largely an intracellular material which can be liberated in quantity when the mold pellicles are broken or bruised mechanically. Helenine, once liberated into the medium, is soluble in water and can be precipitated with acetone.

In attempts to work out the dosage for mice, some interesting observations were made which were of therapeutic importance. One of these was the so-called "plateau effect" of therapy. Once a certain optimal level of dosage was attained, a plateau zone of maximal effect seems to have been reached. Beyond this point the therapeutic effect could not be accelerated by increase in total dosage, or by stepping up the frequency of administration. However, the time at which treatment with Helenine was begun in infected mice was very important. If treatment was delayed beyond six to ten hours after infection, the results of therapy were progressively less effective. However, some therapeutic influence was detectable even when treatment was delayed as long as twenty-four hours following signs of infection. Treatment with Helenine retards marked central nervous system involvement for from twenty-four to forty-eight hours. It is not effective against massive doses of virus, but gives its best therapeutic effect when employed in the treatment of mice infected with from ten to 1,000 fatal doses of virus. Likewise, it would seem that once the infection has passed a certain point of invasiveness, Helenine has little effect, if any, on the course of the disease process.

While the mechanism by which this substance exerts its effect is not

known as yet, the findings suggest that there is some inhibitory action, or "interruption of virus multiplication, slowing down the whole process of infection and spread to the central nervous system." Detailed studies carried out on treated animals and their inoculated controls indicated that Helenine delays the entrance of virus into the brain for a period of from twenty-four to forty-eight hours. In treated animals the amount of virus in the brain, as determined on the third or fourth day of illness, was about 1 per cent of that recovered from the brain in infected animals which were not treated. Thus it appears that the therapeutic effect of Helenine against the virus infections studied may be on an inhibitory basis, or by interruption of virus multiplication within the cells of the host tissue. A second possibility is that the therapeutic agent interferes temporarily with the neuro-invasiveness of the virus.

Another interesting feature of the investigations with Helenine concerned the additive effect of the substance when employed in conjunction with specific virus-neutralizing serum. For example, specific antiviral serum, given forty-eight hours after signs of infection were apparent, had lifesaving effect in mice treated with Helenine, but had no such lifesaving effect on mice in the same stage of infection which were not treated with Helenine. Shope visualizes the action of Helenine in this instance "as that of a virustatic substance prolonging the period during which specific virus-neutralizing serum could exert its virucidal activity."

Another group of investigators (Powell and his associates[2]), actively studying the antiviral potentialities of mold filtrates, has been able to demonstrate that the penicillium mold filtrate, M5-8450, not identified completely as yet, has a chemoprophylactic and chemotherapeutic action against strains of MEF$_1$ poliomyelitis virus (type II), MM virus, and Semliki Forest virus in mice. In the preliminary experiments reported, various routes of inoculation and therapy were employed, and the authors concluded that this particular mold filtrate is effective chemoprophylactically against infection by subcutaneous or intraperitoneal route. The antibiotic filtrate showed its highest effectiveness when administration was begun twenty-four hours before inoculation with virus. Experiments are in progress with a view to ascertaining whether stronger chemoprophylaxis and more prolonged action can be obtained, and whether the oral route of administration for such filtrates would be possible and efficacious.

More recent investigations by this group[3] with the antibiotic filtrate M5-8450 have concerned the inhibition of the cytopathogenesis of poliomyelitis viruses in tissue culture. Strains of all three immunologic types were studied. Monkey testicular cells growing in plasma-clot roller tube culture were exposed to relatively small amounts of the antibiotic M5-8450 twenty-four hours before inoculation with virus. Following this routine, it could be shown that cells so treated were refractory to virus infection, yet viable virus could be demonstrated in the culture medium of these undamaged treated explants for as long as five days after inoculation with virus suspension. When virus suspensions were mixed with antibiotic filtrate prior to inoculation, the inhibitory effect was absent. These observations indicate that the action of M5-8450 is not virucidal, but rather that the substance exerts its effects upon the cells, possibly by interrupting or preventing some stage of intracellular multiplication of the virus. This finding is in accord with the previous observations made in the in vivo tests of this antibiotic filtrate against various neurotropic viruses in mice.

While at the present time such observations do not have practical application with reference to possible means of therapy in the human subject, studies of this type do indicate

that progress is being made toward a better understanding of viral infections.

RUSSELL J. BLATTNER

REFERENCES

1. Shope, Richard E.: An Antiviral Substance From Penicillium funiculosum: I. Effect Upon Infection in Mice With Swine Influenza Virus and Columbia Sk Encephalomyelitis Virus, J. Exper. Med **97**: 601, 1953; II. Effect of Helenine Upon Infection in Mice With Semliki Forest Virus, Ibid., **97**: 627, 1953; III. General Properties and Characteristics of Helenine, Ibid., **97**: 639, 1953.
2. Powell, H. M., Culbertson, C. G., McGuire, J. M., Hoehn, M. M., and Baker, L. A.: Antibiotics & Chemother. **2**: 432, 1952.
Powell, H. M., and Culbertson, C. G.: Action of an Antiviral Mold Filtrate Against MEF, Poliomyelitis Virus in Mice, Proc. Soc. Exper. Biol. & Med. **83**: 161, 1953.
3. Hull, Robert N., and Lavelle, J. M.: Inhibition of Cytopathogenic Effect of Poliomyelitis Viruses in Tissue Culture by Antibiotic M5-8450, Proc. Soc. Exper. Biol. & Med. **83**: 787, 1953.

News and Notes

The following were certified by the **American Board of Pediatrics**, at the examination at Indianapolis, Ind., Dec. 4, 5, and 6, 1953.

Dr. Charlotte Bansmer, 200 15th Ave. North, Seattle 2, Wash.

Dr. John Lane Baskin, 712 N. Travis, Cameron, Tex.

Dr. Paul Baxter, 3725 E. 153rd St., Seattle 55, Wash.

Dr. Karl L. Bergener, 258 E. Court St., Kankakee, Ill.

Dr. Ray E. Burdett, 1448 Oak Ridge Dr., Ogden, Utah.

Dr. Justin David Call, Park Air Force Base, Pleasanton, Calif.

Dr. Merton E. Cohen, 19 N. Second St., Easton, Pa.

Dr. Joseph Deafner Craig, Mayo Clinic, Rochester, Minn.

Dr. William Harvey Crouch, Jr., National Reserve Bldg., Topeka, Kan.

Dr. Bernard Dobrow, 48 E. Santa Clara St. San Jose, Calif.

Dr. James A. Dugger, Topeka Med. Center, 10th Ave. & Filmore St., Topeka, Kan.

Dr. Frank J. Dzurik, 7211 Broadway, Cleveland, Ohio.

Dr. Walter Rather Eberlein, Department of Pediatrics, Massachusetts General Hospital, Boston, Mass.

Dr. Robert J. Ehrenreich, 5015th A.S.U., U. S. Army Hospital, Camp Atterbury, Ind.

Dr. Bernard Etra, 891 Sheffield Rd., Teaneck, N. J.

Dr. Grafton Clinton Fanney, Jr., 21871 Lakeshore Blvd., Euclid, Ohio.

Dr. William J. Farrell, 9801 St. Louis, Evergreen Park, Ill.

Dr. John J. Galligan, 1923 Beechwood Ave., St. Paul 5, Minn.

Dr. Marvin H. Gibstine, 101 S. Meramec, St. Louis 5, Mo.

Dr. Charles Goldenberg, 7100 S. Shore Dr., Chicago 49, Ill.

Dr. Robert E. Gustafson, Jr., The Kankakee Clinic, Volkmann Bldg., Kankakee, Ill.

Dr. Hyland J. Hebert, 516 M. H. del Pilar, Manila, Philippines.

Dr. Wayne Iren Herbert, 726 N. Pickering Ave., Whittier, Calif.

Dr. Robert Marshall Hidey, Jr., USNCS, Navy No. 926, FPO San Francisco, Calif.

Dr. Hubert Rex Holland, 2535 Madison Ave., Paducah, Ky.

Dr. Elizabeth K. B. Jerome, 328 E. Hennepin St., Minneapolis, Minn.

Dr. Peter Ben Kamin, 2128 45th St., Galveston, Tex.

Dr. Richard Sterling Kelly, Jr., Box 3323, Fayetteville, N. C.

Dr. John Hawks Kennell, Babies' and Children's Hospital, 2065 Adelbert Rd., Cleveland 6, Ohio.

Dr. Vernon Kores, 945 N. 12th St., Milwaukee 3, Wis.

Dr. Herman Otis Krempin, 1511 N. Beckley St., Dallas, Tex.

Dr. Howard V. Kuder, 1208 N. Walnut St., Muncie, Ind.

Dr. Marion Kenneth Ledbetter, 1453 S. Quaker, Tulsa, Okla.

Dr. John Franklin Leeds, The Butler Clinic, Hot Springs, S. D.

Dr. Palmer O. Lundeberg, 2847 N. Austin Ave., Chicago 34, Ill.

Dr. Jack Markovitz, 3507 W. Lawrence Ave., Chicago 25, Ill.

Dr. John Robert Maxwell, Station Hospital, Camp Stoneman, Calif.

Dr. Kenneth Cochran Mickle, 704 S. Van Buren St., Green Bay, Wis.

Dr. Loren V. Miller, 315 Nepperhan Ave., Yonkers 2, N. Y.

Dr. Henry Mitchell, 312 E. School St., Indiana, Pa.

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Dr. Mervyn U. Schwartz, Tacoma Indian Hospital, Tacoma, Wash.
Dr. Samuel Sepkowitz, Pasteur Medical Bldg., Oklahoma City, Okla.
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Dr. Sterling B. Suddarth, 13706 Bancroft, San Leandro, Calif.
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Dr. William West Thompson, 570 Graham Rd., Fort Sam Houston, Tex.
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Dr. William Arthur Tomlinson, 1821 S. First St., Springfield, Ill.
Dr. Kenneth J. Winters, 1411 Wauwatosa Ave., Wauwatosa 13, Wis.

The following oral examinations will be held by the Board:

Washington, D. C., Feb. 19, 20, and 21, 1954.

Des Moines, Iowa, March 19, 20, and 21, 1954.

Pediatricians are invited to attend a meeting of the **American College of Allergists** at Miami Beach, April 5 to 10, 1954. The program contains an evening panel discussion on "Allergy in the Infant Under Two," a pediatric luncheon program on gastrointestinal allergy, and a general session on the morning of April 9 devoted to papers on pediatric allergy.

The 10th M & R Conference, sponsored by the M & R Laboratories of Columbus, Ohio, was held November 19, 1953, under the auspices of the Department of Pediatrics of the State University of Iowa. The subject of the conference was "The Role of Vitamin B_6 in Human Nutrition." A group of outstanding authorities on the fundamental scientific aspects of the role of vitamin B_6 in metabolism and its application to clinical problems was assembled for this conference. Particular attention was given to the problem of the occurrence of convulsions in infants which have been attributed to a deficiency of vitamin B_6. A summary of the papers presented and the discussions will be published for distribution to the profession. The conference was conducted under the chairmanship of Dr. Charles D. May, professor and chairman of the Department of Pediatrics of the State University of Iowa.

A pamphlet on "Standards of Care for Cleft Palate Rehabilitation Centers in Hospitals" has been issued by the Bureau of Dentistry of the New York City Health Department. Eighteen pediatricians and ten dentists served in an advisory committee in the preparation of the standards. The "Standards" consider such questions as personnel, physical plant, and the general program of oral surgery, speech training, parent counseling, and other factors which are interrelated in the care of a child with a cleft palate. Copies may be obtained from the Bureau.

Fellowships for training in clinical investigation in the field of cancer in children, including chemotherapy, have been created at the **Children's Cancer Research Foundation.** Stipends vary from $2,400 to $5,000, depending upon training. Application blanks may be secured from the office of Dr. Sidney Farber, Scientific Director, Children's Cancer Research Foundation, Boston, Mass.

Book Reviews

Prematurity, Congenital Malformation, and Birth Injury. Proceedings of a Conference in New York, June, 1952. New York, 1953, Association for the Aid of Crippled Children, 255 pages.

The report of an interesting two-day conference in which some thirty well-known scientists working on the problems in these three fields participated. For example, in the discussion on prematurity, among the subjects presented were respiratory exchange by Clement A. Smith, immunology by Dancis, the development of the enzyme system by Himwich and Najjar, and endocrinology by Jailer and Lanman. In the discussion on congenital malformations, particular stress was placed on the experimental work being carried on by Ingalls and others. The discussion of birth injury was centered on such problems as anoxia, and the placental transfer of oxygen. The conference was informal, and the discussions and questions from the floor in which many participated add much to the interest and value of the report. It gives a good picture of the many fundamental problems underlying the three subjects discussed, and of the experimental studies which are being carried on in many places. Conferences of this type, which give an opportunity for the exchange of ideas, are of great value to those attempting to solve the underlying problems in a particular field. The report is better edited and presented than many similar conference proceedings.

Mongolism. A Clinicogenealogical Investigation. Jakob Øster, Copenhagen, 1953, Danish Science Press, Ltd., 206 pages. Price $3.00.

A monograph, excellently translated from the Danish, reporting a study of 526 living mongols on Seeland and neighboring islands. The material, started in 1923, is based on a register of 1,006 mongols, of whom 480 had died. Not only were the cases examined personally by the author, but extensive data were gathered as to the mother's pregnancy and the family history. The study, which was aided by a grant from the Rockefeller Foundation, is an interesting and important addition to the subject of mongolism. Only a part can be covered in a review.

While about one-fourth were under 5 years, forty were over 40 years of age. Mentally they included imbeciles, some idiots, and a few feebleminded. Few learn to read or write and probably none learn to do sums. A failing memory for abstract things was noted which makes for difficulty in vocational training. As a rule, the mongols were good natured, fond of play, and imaginative, but some were stubborn and had developed troublesome behavior problems. No relationship was found between the degree of mental deficiency and the number of physical stigmas.

The frequency of mongoloid stigmas in the group was compared with a group of 278 nonmongoloid defectives. Øster considers ten stigmas as cardinal signs of mongolism, and states that if four or more of these are present in a mentally defective, the diagnosis is probably mongolism. These ten signs in order of importance are: (1) Four-finger line across the palm of the hand, (2) short, crooked fifth finger, (3) short broad hand, (4) hyperflexability, (5) oblique eye slits, (6) epicanthus, (7) furrowed tongue, (8) irregular abnormal teeth, (9) narrow, high palate, (10) brachycephaly. Nos. 7 and 9 are not applicable to infants, and epicanthus tends to disappear as the mongol grows older. He is in sharp disagreement with Aldrich's contention that a mongol can always be diagnosed in the neonatal period.

From his studies he concludes that it is not an hereditary disease, but one due to exogenous factors resulting from the mother's depressed reproductive faculty. His studies bear out the well-known advanced age of the mother as being important. He found further a long interval between marriage and pregnancy, and that the intervals between and after the birth of a mongol were longer than between normal births. He could find no particular abnormal conditions during the pregnancy, but noted a "remarkable accumulation" of abdominal diseases and operations in the period three years before to five years after the birth of the mongol. The discus-

sion of twins is quite complete. Monozygous twins usually show concordance and dizygous discordance. Six families in his series had two mongols of the same sibship. This he considers statistically unimportant.

Throughout the text there is a constant reference and discussion of the studies and ideas of others as to the point under discussion, and the bibliography contains some 300 references. It is an excellent monograph and the author's studies are unusually well presented. The summary and conclusions are fully in keeping with the facts disclosed in the study.

Have Fun . . . Get Well! Maryelle Dodds, New York, 1953, American Heart Association, 39 pages.

A small booklet that the practitioner might well keep in mind. Its purpose is to give parents of children with rheumatic heart diseases ideas and suggestions which will help keep the bedridden children more contented. It covers in two sections the teen-agers and younger children. The book itself does not go into detailed techniques, but rather makes suggestions and furnishes ideas and gives references to more complete texts on such subjects as carving, jewelry making, leather work, weaving, plant and animal care, etc. The booklet may be obtained by physicians through the affiliated state and local associations of the American Heart Association.

Dystrophia musculorum progressiva. Prof. Dr. P. E. Becker, Stuttgart, 1953, Georg Thieme Verlag, 311 pages. Price D.M. 28.50.

This monograph on progressive muscular dystrophy presents the genetic and clinical studies by Prof. Becker of Tuttlingen. The author considers the shoulder girdle type and the pelvic girdle type to be distinct genetically. The first he considers due to a dominant trait and the second to a recessive trait. In the second half the author presents the genealogy of sixty-three carefully studied families in relation to the presence of the disease. The book is of particular interest to those interested in genetics.

Lecciones de terapeutica infantil. Juan P. Garrahan and Collaborators, Buenos Aires, 1953, Libreria "El Ateneo," 619 pages.

A second edition of the pediatric text in Portuguese by Dr. Garrahan, director of the Institute of Pediatrics and Periculture in Buenos Aires. A large group of Brazilian physicians have contributed in special fields.

Personal Fitness. Merit Badge Series, Boy Scouts of America. J. Roswell Gallagher, M.D.

This is a pamphlet on physical fitness for boys 11 years of age and older with which the pediatrician should be familiar. It contains a more common-sense discussion of such factors as diet, rest, exercise, etc., which form the basis of physical fitness, than we believe is otherwise available. Dr. Gallagher has been the chief advisor in its preparation but a number of others have taken part. It is written in clear nontechnical language that a boy can understand. Problems of growth and certain common diseases are included. It is one of a series of about 100 pamphlets prepared in the Merit Badge Library of the Boy Scouts and sells for 25 cents. Whether or not a boy is a Scout, it is a valuable book to put in the hands of a boy in pre- and early adolescent period when athletic activities begin to play such an important part in his development.

Year Book of Pediatrics—1953-1954 Series. Edited by Sydney S. Gellis, M.D., Chicago, 1953, Year Book Publishers, 435 pages. Price $6.00.

In the latest edition of the *Pediatric Year Book*, covering the period from June, 1952, to May, 1953, Dr. Gellis has made an excellent selection of the pediatric studies and reports for the period covered. Not the least important service is the comment attached to many of the reviews. For many of these the editor has turned to well-known authorities in some special field. The book measures up to previous volumes in the series.

Editor's Column

THE TONSIL PENDULUM

THE older practitioners will remember the tonsillectomy era of roughly 1910 to 1930, when, at least so far as children were concerned, the tonsils were looked upon by some as the root of all evil. Some school physicians seriously reported finding up to 60 to 70 per cent of young school children with diseased tonsils. Size and disease were commonly confused. The "T and A day" held several times a week in the hospitals was a Roman Holiday, with children lined up waiting for their turn weeks in advance, and even worse was the "Tonsil Day" in smaller communities, where up to thirty or more children would be collected in a makeshift hospital, and a visiting otolaryngologist from the big city paid a visit and operated upon children he had never seen before. This atrocity was even carried out under the guise of a "public health program." The attitude and thought of parents in this era, for which the medical profession was largely responsible, are well illustrated by the story of an intelligent mother who appeared one day in her pediatrician's office with her 6-year-old boy, an only child.

Mother (sighing): "Well, I've got up my courage to have it done."

Doctor: "Have what done?"

Mother: "Have Tommy's tonsils out."

Doctor: "But why have Tommy's tonsils out? I don't recall any tonsil trouble."

Mother: "Why I thought every child had to have his tonsils out."

Those days, we are happy to say, are over. As a result of the studies and data presented by Kaiser and others, the indiscriminate, unnecessary T and A operation fell into disrepute. In the revolt against T and A operations, perhaps the pendulum has swung too far the other way, as so often happens. This is the question that Johnston and Watkins raise in a report of their experiences on page 127 of this issue. Every practitioner can recall instances where the picture of a poorly nourished child in ill health changed rapidly and completely following a T and A operation. The removal of a focal infection, even when it does not produce a febrile reaction, results in increased storage of nitrogen and calcium, and the weight gain represents an acquisition of body tissue. He will also recall some patients where a tonsillectomy did not change the picture in the slightest way.

The point is that a T and A operation is a matter that must be individualized just as much as an appendectomy. No physician would advise an appendectomy simply because a child complains of a pain in the belly and the physician cannot determine the cause. The mere fact that a child is in poor health, or, as all children do, has occasional throat infections, is not an indication for a tonsillectomy. When tonsillectomy is advised, it must be based on the fact that in this

particular child the tonsils are diseased, and, all other causes having been eliminated, can in all probability be looked upon as the cause of the ill health. Then a T and A is not only justified, but advisable.

* * * * *

While on the subject of tonsils, it is interesting to note that the question of the relationship between bulbar polio and tonsillectomy is again coming up. A few years ago there was much argument and many articles were written discussing this relationship. While a tonsillectomy does not predispose to polio, it became generally accepted that a tonsillectomy *within a few weeks* before a child contracted the disease predisposes to the severe bulbar type of the disease; hence, the current teaching and practice that tonsillectomy, an elective operation, should not be done if polio is present in the community. Trauma is considered as playing an important part in this predisposition.

In 1944 Lucchesi and La Boccetta,[1] in a study of the records of 426 cases of polio in a Philadelphia hospital, noted a higher incidence of bulbar involvement in those patients who had no tonsils than in those who still possessed their tonsils. Seventy-eight per cent of those who died from the disease had no tonsils or adenoids when they became ill. For some reason or other the significance of this observation was generally overlooked until Top[2] in 1952 reported on a series of 1,947 patients from a Detroit hospital. He found an even higher incidence of bulbar involvement in patients who had no tonsils at the time the disease was contracted, regardless of the time of the tonsillectomy. There was a fatality rate of 93.5 per cent for the bulbar cases which had no tonsils.

In last month's issue of the JOURNAL (page 14), Weinstein, Vogel, and Weinstein[3] reported on a study of 800 cases from a Boston hospital, which was undertaken to see whether or not the same findings applied to the patients observed by them. Their figures closely paralleled those of Top. They reached the conclusion that absence of tonsils and adenoids increases the susceptibility to the development of bulbar and bulbospinal polio, even if the tonsillectomy had been done years earlier. They feel that the question of the effect of recent tonsillectomy must be evaluated in terms of the increased susceptibility incident to the absence of tonsils and adenoids.

Seemingly it would appear from these studies and reports that it may be the absence of tonsils and adenoids (perhaps the loss of a filter so to speak), rather than the trauma of a recent tonsillectomy, that predisposes to an increased incidence of bulbar involvement in individuals who are exposed to the polio viruses. So the polio-tonsillectomy question and problem rises anew.

REFERENCES

1. Lucchesi and La Boccetta: Am. J. Dis. Child. **68**: 1, 1944.
2. Top: J. A. M. A. **150**: 534, 1952.
3. Weinstein, Vogel, and Weinstein: J. PEDIAT. **44**: 14, 1954.

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